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The Journal of Laboratory and Clinical Medicine

VOL. IV. ST. LOUIS, FEBRUARY, 1919 NO. 5

ORIGINAL ARTICLES

THE LESIONS OF THE RESPIRATORY AND GASTROINTESTINAL TRACTS PRODUCED BY MUSTARD GAS (DICHLORETHYL-SULPHIDE)*

BY ALDRED SCOTT WARTHIN, PH.D., M.D., AND CARL VERNON WELLER, M.S., M.D., ANN ARBOR, MICH.

I. LESIONS OF THE RESPIRATORY TRACT

THAT irritation and inflammation of the upper respiratory tract, terminating in pneumonia, can be experimentally produced in animals by mustard gas was demonstrated in 1886 by Victor Meyer, the discoverer of this chemical entity. After its introduction into military use by the Germans, in the present war, the irritant effects of mustard gas upon the mucous membranes of the respiratory tract were noted by medical observers in the Allied Armies. The earlier British Army reports describing the respiratory symptoms produced by exposure to mustard gas speak of an initial tendency to sneeze, with gradually increasing nose and throat irritation, followed in about twelve hours by a free discharge of mucus from the nose. Prolonged exposures, even to slight concentrations, were observed to cause laryngitis and aphonia, even severe enough to put the men out of action. In the more severe cases bronchitis and pneumonia were found to develop thirty-six to forty-eight hours after the exposure. Ulceration of the mucous membranes of the respiratory passages may be so extensive and severe as to cause death in themselves or a fatal bronchopneumonia may follow. About 95 per cent of the men gassed with mustard gas showed involvement of the respiratory tract.

Giraud (*Journal de Médecine et de Chirurgie Pratiques*, 1917, lxxxviii, 890)

*From the Pathological Laboratory, University of Michigan, Ann Arbor, Michigan.

found that symptoms of involvement of the respiratory tract in the form of aphonia, coughing, tracheitis and bronchitis were, next to the eye lesions, the most common affections produced by exposure to mustard gas. *Mandel and Gibson* (*Journal American Medical Association*, 1917, p. 247) describe the respiratory symptoms of mustard gassing as an "irritative, noninflammatory, nonfebrile" laryngitis and bronchitis, with a feeling of constriction about the larynx, tightness of the chest, aphonia, and paroxysmal cough, particularly severe at night, with a serous discharge in the mild cases, hemorrhagic expectoration in the most severe, and purulent in the late stages complicated by bronchopneumonia. The physical signs are those of a diffuse bronchitis. The chief complications are pulmonary edema and a relatively late bronchopneumonia.

Pissarello (*Giornale di Medicina Militare*, 1918, lxvii, p. 128) describes the respiratory affections in mild cases of mustard gassing as coryza, dryness of throat and hoarseness, while in the more severe cases the hoarseness may pass into complete aphonia, with congestion and tumefaction of the pharyngeal mucosa, swollen uvula, and spots of whitish-gray exudate over the pharyngeal mucosa. He noted a laryngotracheitis only in the most severe cases, with occasional extension to the bronchi, with rales, or the production of atelectatic areas. In only two cases did he find a bronchitis with subfebrile state.

Rendu (*Lyon Médical*, March, 1918, p. 108) gives the most complete clinical description of the lesions of the upper respiratory tract caused by exposure to mustard gas, with a series of figures showing the location of the lesions in the nose, pharynx and larynx. The nasal symptoms were coryza lasting from one to five days, with a serous discharge, and epistaxis in one-eighth of his cases, and very frequently a diminution or complete loss of the senses of taste and smell. Rhinoscopic examination showed usually only a congestion of the mucosa, but in some cases small whitish ulcers were present at the level of the anteroinferior portion of the septum, or at the head of the inferior turbinate. The chief symptom referable to the pharynx was dysphagia, appearing usually about the second to third day and lasting about four to six days, but in some cases more severe and of longer duration. The objective symptoms were redness of the mucosa accompanied by a turgescence of the uvula and the posterior pillars. In about 15 to 20 per cent of the cases seen, localized whitish diphtheritic necroses were noted upon the pharyngeal mucosa, particularly upon the uvula and the neighboring borders of the pillars, but also on the posterior pharyngeal wall in its median portion, or behind the posterior pillars. In the most severe cases the diphtheritic eschars covered the entire posterior wall of the oropharynx and the laryngopharynx. Rendu found laryngotracheal symptoms to be the most common manifestation of the action of mustard gas in the upper respiratory tract. The subjective symptoms were sensations of tickling, dryness or burning, localized in the region of the larynx and behind the sternum, lasting for several days or weeks according to the intensity of the lesions of the mucosa. Coughing was constant and very painful, appearing about the same time as the laryngeal symptoms just described; it was dry, paroxysmal and was most troublesome at night. In about one out of ten cases there was for several days a blood-streaked expectoration. The voice was rough or husky

in 60 to 70 per cent of cases, and a complete aphonia occurred in about 30 to 40 per cent. The vocal symptoms disappeared very slowly as a rule. Rendu observed no symptoms of laryngeal spasm or edema. The laryngoscopic examination showed changes in the laryngeal mucosa ranging from a more or less marked hyperemia, accompanied by a tumefaction of the arytenoids and ventricular bands and the folds of the posterior commissure, to the development of whitish eschars, like those in the pharynx, localized at different places in the mucosa. He describes the development of the eschars as follows: During the first three or four days only the hyperemia of the mucosa is noted; the laryngoscopic examination is often difficult because of the abnormal intensity of the pharyngolaryngeal reflexes. From the fourth to the seventh day the necrosis of the mucosa begins to show in grayish or whitish patches resembling a false membrane. These eschars were observed most frequently at the vertex of the arytenoid pyramids, the border of the epiglottis, and the free border of the vocal cords, associated as follows: epiglottis and arytenoids, cords and arytenoids, and epiglottis, cords, and arytenoids. The most frequent lesions of all were the isolated eschars of the vocal cords which were arranged symmetrically on the anterior two-thirds of the free borders of the cords in the form of an elongated segment, sharply delimited on its external border, but somewhat irregular on its internal. The eschars are creamy white in color, while the remainder of the cord is deep red. The healing of these lesions is very slow, and requires several weeks. The *tracheal* lesions are analogous to those of the larynx; their subjective symptoms are more or less confounded with those of a bronchitis so often coexistent with it.

In the few reported autopsy findings in cases of death resulting from mustard gas the lesions of the respiratory tract are not very fully described. *Canelli*, in one case, observed a diffuse tracheitis, bilateral subacute bronchitis, pulmonary hypostasis with acute diffuse edema, and a localized fibrinoadhesive pleuritis. *McNee*,* in summing up autopsy findings, states that the respiratory tract lesions were acute inflammation of the air passages, desquamation of the mucous membranes and formation of false membrane, to which may be added infection in the form of acute purulent bronchitis, with atelectasis and bronchopneumonia. Emphysema may also be present. *Dunn** in four autopsies found the chief lesions to be severe damage to bronchi and bronchioles, persistent edema, and severe infection of respiratory tract, bronchopneumonia, and in two of the cases, hemorrhagic exudations. *Karsner* (*American Journal of Medical Sciences*, 1918, clv, 904) noted the following respiratory lesions in four autopsies following death from mustard gassing: Mucous membranes of nose and pharynx were the seat of a marked mucous inflammation. Larynx, trachea and bronchi showed severe inflammation, in one case with pseudomembrane formation, in two others with multiple necroses of the mucosa. In two cases there was an acute fibrinous pleurisy. All cases showed a bilateral bronchopneumonia with slight general edema of the lungs. *Rendu* records that in two autopsies the laryngotracheal mucosa, completely necrosed, was detached in shreds like a false membrane.

The animal experiments of *Kolls* and *Gilbert, Raper* and *Ball, Marshall*

*For references, see Jour. Lab. and Clin. Med., 1918, iii, No. 8, p. 454.

and *Miller*,* and others have shown that mustard gas produces in exposed animals coryza, pharyngitis, salivation, tracheal rattle, congestion of the tracheal mucosa, bronchitis and bronchopneumonia. In the *United States Naval Bulletin*, April, 1918, there are some color plates of the gross pathologic changes in trachea and larynx of a dog dying forty-eight hours after a thirty-minute exposure to a 0.13 milligram-liter concentration of mustard gas. Edema and congestion of epiglottis and glottis, and an acute membranous tracheitis are shown. A section of lung from another dog shows atelectasis and patches of focal pneumonia following a thirty-minute exposure to 0.056 milligram-liter concentration. Plate V shows similar tracheal and pulmonary conditions.

The pathologic changes in the respiratory tract described above are chiefly those noted in clinical and gross pathologic observations. At this time no published reports in the general literature exist in which the detailed microscopic pathology of the respiratory tract lesions of dichlorethyisulphide gassing are given. It is the object of this paper to present such a statement of the minute pathology of these lesions, in such a way as to give a complete picture of the process from the mildest type of lesions to the most severe.

METHOD

In our gassing investigations we have made use of a simple apparatus, which has served our purposes most effectively and is to be recommended for its

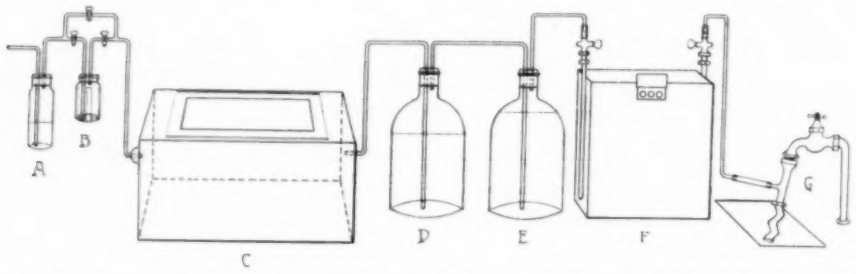

Fig. 1.—Experimental Gassing Apparatus. (Pathological Laboratory—University of Michigan.) A, Washer containing sulphuric acid; B, Gas container; C, Gassing box; D and E, Degassing bottles; F, Standard gas meter; G, Suction pump.

simplicity, as well as for the relative accuracy with which the gas concentration can be estimated. As shown in Fig. 1, it consists of:

A, one or more bottles containing sulphuric acid for drying the air admitted.

B, a container for the liquid mustard gas so arranged as to be easily detached from the tubing, so that when stoppered with a ground glass stopper, it can be weighed with its contents. Above this is a shunt tube for varying the amount of pure air admitted to the chamber, thus varying the concentration of gas obtained. Within the mustard gas bottle strips of absorbent paper are so arranged as to increase the evaporation surface. When used for experimental work with toxic substances, which are gaseous at room temperature, the gas intake replaces this weighing bottle.

C, a gassing chamber which is large enough to hold several small animals

*For references, see Jour. Lab. and Clin. Med., 1918, iii, No. 8, p. 454.

or a large dog. It has a removable plate glass top, so that the animals can be observed during gassing; this is sealed during the experiment with the gutta-percha-tallow mixture, commonly used for making air-tight seals for museum jars, and may be held in position by a heavy weight, if necessary.

D and *E*, bottles for removing the gas from the air flowing from the chamber, so that the amount passing over can again be estimated here if desired. When used for mustard gas these bottles may contain a chlorinated solution for the destruction of the gas.

F, a standard gas meter for measuring the amount of air passing through the chamber.

G, a suction pump attached to the city water supply.

After detaching the weighing bottle air is drawn through the gassing chamber for some time in order to wash out the mustard or other gas remaining. The weight of mustard gas used is obtained by difference and the amount of air drawn through during the period in which the bottle is attached is recorded from the gas meter. The concentration represented by these figures is obtained by reference to a transformation table. The results are as approximately correct as can be obtained by any other form of gassing chamber, and the apparatus has the advantage of simplicity. As far as mustard gas is concerned, such factors as variable absorption by the hair of the animal, etc., introduce unavoidable errors, so that absolute accuracy of method can not be obtained, regardless of the limitations of the apparatus.

The animals were killed by direct blow upon the neck to avoid the changes in the respiratory system produced by an anesthetic. Autopsies were made as quickly as possible after the death of the animal. The tissues were fixed in formol, were embedded in paraffin and the usual stains, hematoxylin and eosin, etc., were employed.

GROSS AND MICROSCOPIC PATHOLOGY

Various series of animals were exposed to varying concentrations of mustard gas in the gassing chamber for varying periods of time. It was found that rabbits would survive a forty-minute exposure to a dilution of 1:110,000, recovery taking place after a period of respiratory involvement. For purposes of brevity typical protocols have been selected and are given here.

RABBIT 32.—Exposed in the gassing chamber for forty minutes to a 1:110,000 concentration. During the gassing the rabbit frequently changed position, rubbed its nose, and showed signs of irritation. When removed from the gassing chamber the rabbit appeared unaffected in any way. In two and one-half hours conjunctival erythema and increased lacrimation were evident, these symptoms increasing until the animal was killed. Seven and one-half hours after removal from the box, symptoms of coryza manifested themselves. Twelve hours after removal from gassing chamber, rabbit was killed by blow upon the neck. The conjunctivæ presented marked congestion and edema, and were covered with purulent flakes. The bulbar conjunctivæ showed a marked collar of edema at the limbus. The cornea showed a slight haziness, and at its vertex there was a definite necrosis of the superficial epithelium. This area was irregularly oval in shape. The lid margins showed marked congestion and the skin about mouth and nostrils was erythematous.

Autopsy showed right-sided dilatation of the heart. No fluid was found in the pleural cavity, and there were no pleural changes. On section the lungs showed marked congestion and edema without hemorrhages or atelectasis visible to the naked eye. No

Fig. 2.—Section of laryngeal mucosa. Rabbit 31. Exposed thirty-five minutes to a concentration of 1:30,000. Killed thirty hours after gassing. Pyknosis and mucoid degeneration of the epithelium. Marked congestion and edema of the submucosa.

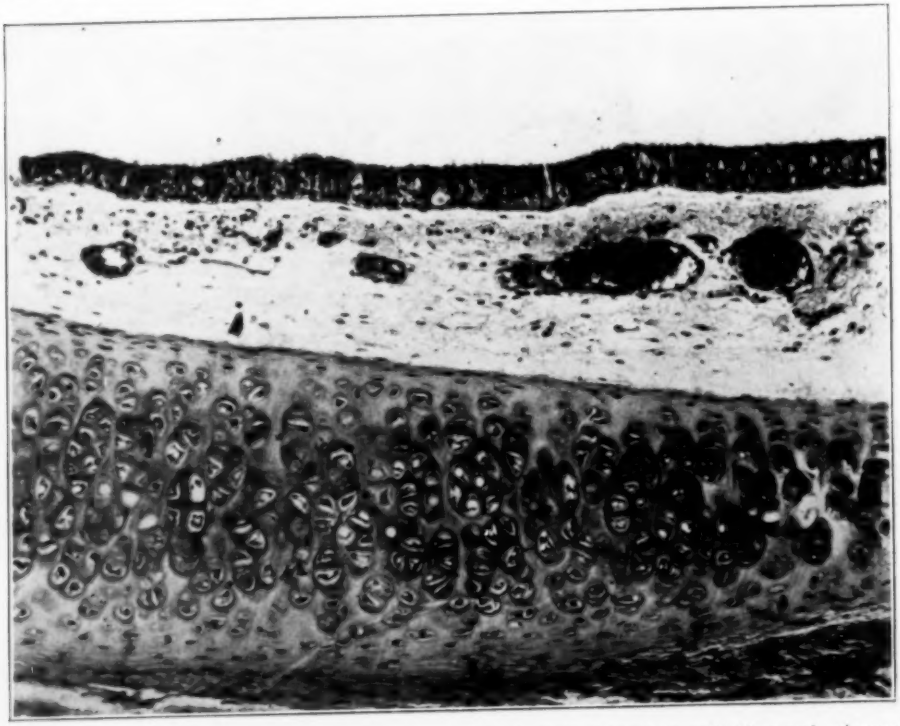

Fig. 3.—Section of tracheal wall of same rabbit as Fig. 2. Similar changes in epithelium and submucosa.

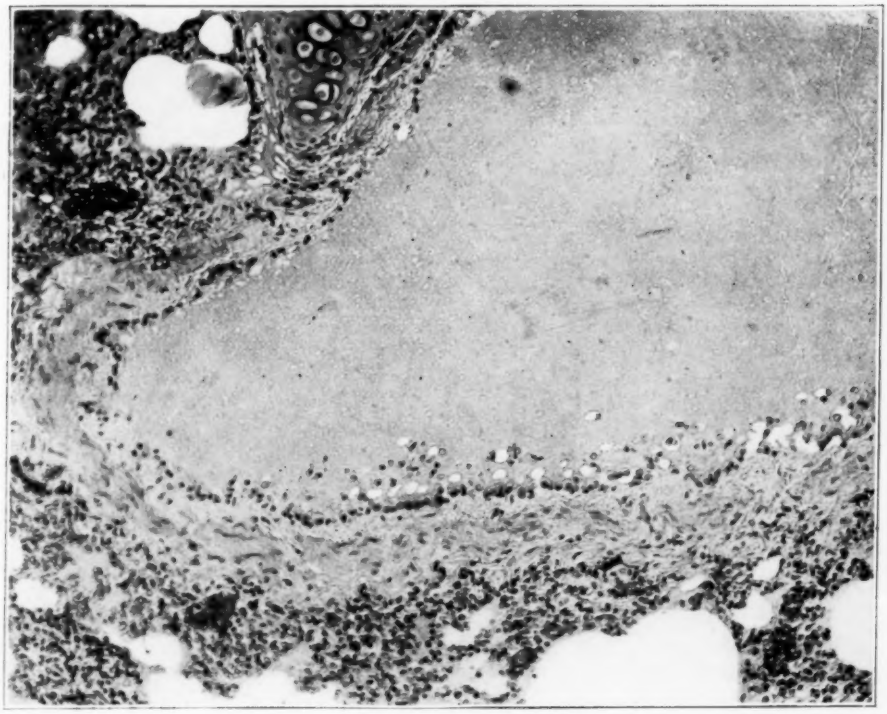

Fig. 4.—Rabbit 30. Exposed thirty minutes to a concentration of 1:15,000. Killed four and one-quarter days after gassing. Section of larger bronchus showing lumen filled with edema fluid. Bronchial epithelium shows marked mucoid and hydropic degeneration.

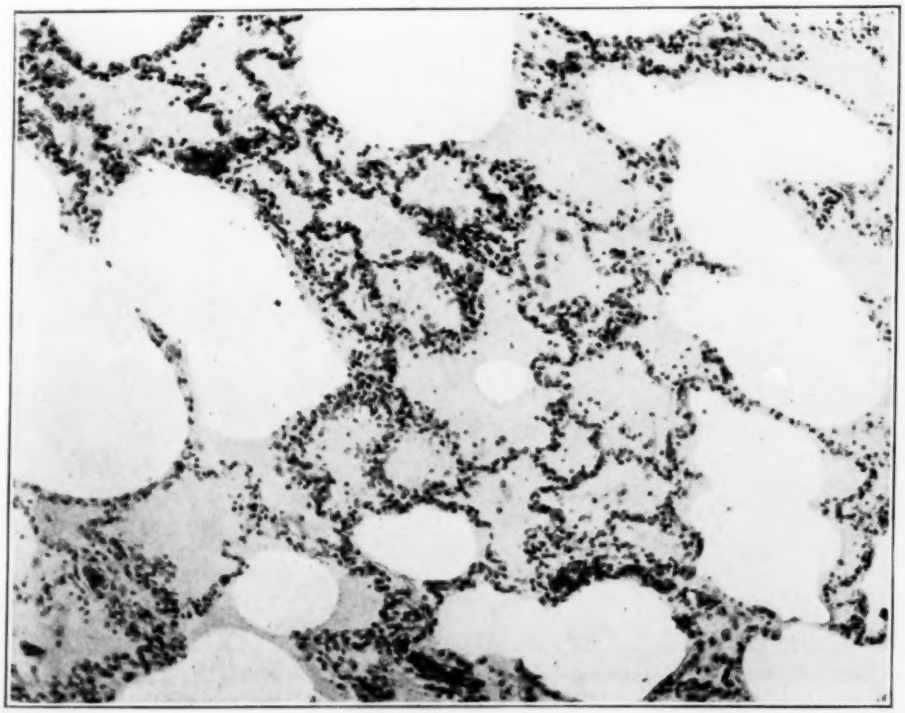

Fig. 5.—Lung of same rabbit as Fig. 4. Acute congestion and edema.

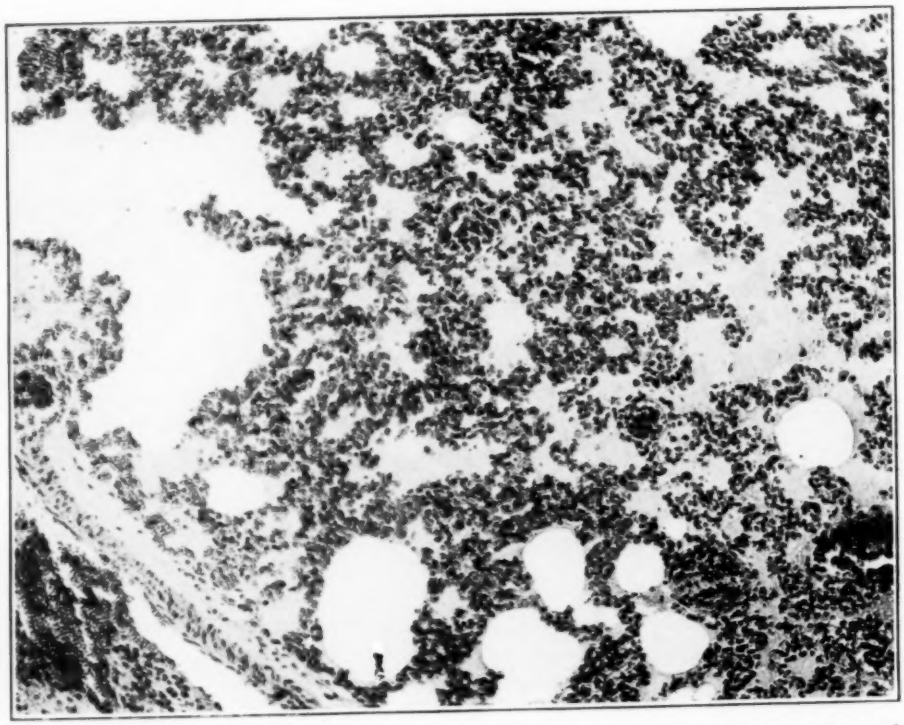

Fig. 6.—Rabbit 32. Exposed forty minutes to a 1:110,000 concentration. Killed twelve hours after removal from gassing chamber. Section of lung. Marked congestion, edema, and areas of partial atelectasis alternating with those of emphysema.

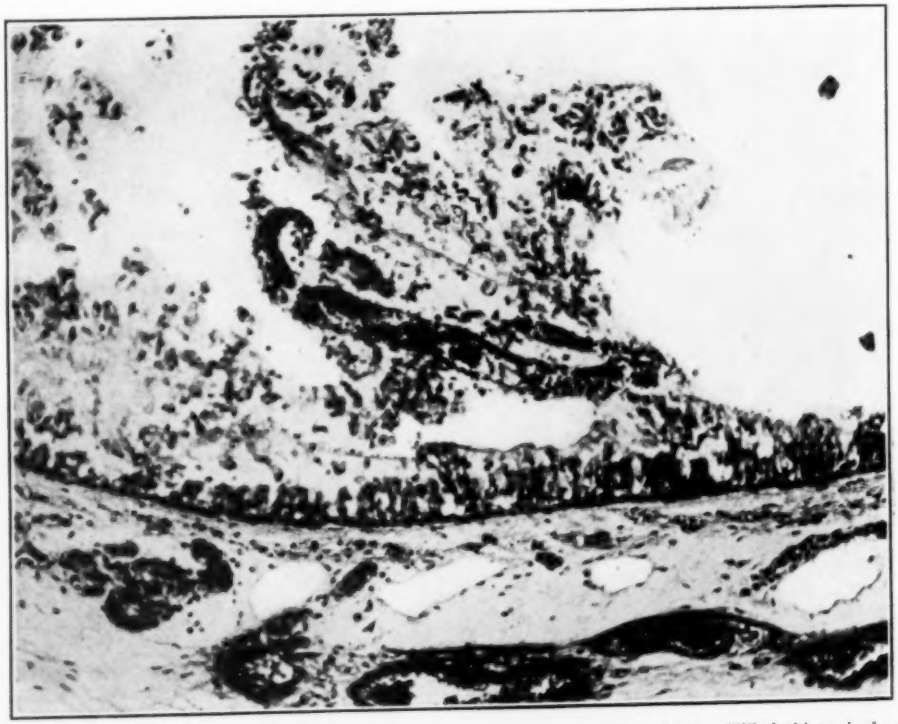

Fig. 7.—Rabbit 33. Exposed twenty minutes to a concentration of 1:15,000. Killed thirty-six hours after gassing. Section of trachea showing acute catarrhal desquamative tracheitis; marked mucoid degeneration of the epithelium; congestion and edema of the submucosa. Lumen filled with mucus containing many desquamated cells.

differences between upper and lower lobes were noted. The trachea was filled with frothy mucus and the mucosa was congested, particularly in the upper portion, the congestion diminishing below toward the bronchi. The mucosa of the entire upper respiratory tract, nose, mouth, pharynx and larynx showed congestion without hemorrhages.

Microscopic Findings.—Nose. Sections from the skin about the nostrils show slight pyknosis of the epidermis and congestion of the vessels, without other changes. The mucous membrane of the nose shows a marked congestion, more marked pyknosis of the epithelium and slight edema. Sections from the *pharynx and larynx* show a marked congestion with extreme mucous degeneration of the mucous glands. There is pyknosis of the upper layers of epithelium of the mucous membrane but no definite necrosis. The acini of the mucous glands are greatly enlarged and filled with deep blue-staining mucus. The ducts are dilated and filled with mucus. There is but slight edema of the mucous membrane and no hemorrhages. These signs diminish in the *trachea* except for the edema, which is somewhat greater in the lower part of the trachea than above, and there is an increased number of wandering cells in the mucosa. The columnar cells of the tracheal mucosa show more marked changes than the squamous epithelium of the upper respiratory tract. The great majority show a hydropic or a mucoid degeneration. The epithelium is intact for the greater part but small patches of desquamation occur. The larger *bronchi* present the same appearance as the trachea, though to a somewhat lesser degree. The smaller bronchi are filled with mucus. The epithelium shows mucoid degeneration and occasional areas of desquamation. The walls of the larger bronchi are edematous, the vessels markedly congested, but there is no increase in leucocytes. The exudate in the bronchi is entirely mucoid or albuminous in character, not fibrinous. There is no hemorrhage into the bronchi. The *lung* tissue shows extreme congestion and marked edema, with numerous minute hemorrhages, too small to be seen with the naked eye (see Fig. 6). A majority of the alveoli are filled with a heavy albuminous precipitate, but scattered throughout the lung are numerous emphysematous alveoli and dilated bronchioles. No areas of complete atelectasis are seen, although edematous areas show partial collapse.

The changes in the respiratory tract of this animal are those of an acute catarrhal rhinitis, pharyngitis, laryngitis, tracheitis and bronchitis, decreasing somewhat in intensity from above downwards, with pulmonary congestion and edema.

RABBIT 33.—Exposed twenty minutes to a concentration of 1:15,000. During the exposure the rabbit changed its position from that of facing the inflowing mustard gas to the opposite direction. Three hours after removal from the gassing chamber the animal showed increased lacrimation in both eyes. The borders of the eyelids, skin areas about the mouth and nostrils, the ears and all parts of the body where the hair was short and thin exhibited a marked erythema. The animal showed marked photophobia and irritation of the eyes. Eight hours after removal from the chamber flakes of purulent material were seen over the conjunctivæ and a definite coryza had developed. The conjunctivæ were edematous and congested. These symptoms increased for thirty-six hours, when the animal was killed.

Autopsy showed a severe conjunctivitis and coryza. Right-sided dilatation of the heart. The upper air passages were filled with foamy exudate and the mucosa was congested. Pleural cavities and pleuræ negative. The lungs were markedly congested, the right lung more so than the left. The lungs appeared air-containing throughout, except for the midddle lobe on the right, which was solid in areas, dark red in color. On section it bled but slightly. Beyond congestion no other changes were found in any organs or tissues.

Microscopic Findings.—The cutaneous borders of the *nostrils* show necrosis, edema, congestion and marked leucocyte infiltration of the corium. The mucous membrane of the nose presents patches of necrosis of the epithelium, congestion and edema, areas of small-celled infiltration of the submucosa, and marked mucous degeneration of the mucous glands. *Mouth and pharynx.* Sections of tongue and pharyngeal wall show a contraction of the upper half of the squamous epithelium with pyknosis of the nuclei, congestion of the vessels, slight edema of the submucosa and slight small-celled infiltration. The *larynx* presents patches of necrosis in the hyperemic mucous membrane with marked edema extending to the cartilages. Small-celled infiltration is well marked. Mucous glands

show marked mucoid degeneration. The surface of the mucosa of the *trachea* is covered with patches of mucus containing desquamated cells. The epithelium shows marked mucoid and hydropic degeneration; there are large areas of complete necrosis with desquamation. In the submucosa there is a marked edema extending to the cartilage rings. The vessels are markedly congested (see Fig. 7). The larger *bronchi* show marked degeneration and necrosis, and desquamation of the epithelium, the epithelium being represented for the greater part by a single line of nuclei at the base. Many of the bronchi are filled with an exudate of mucus containing many desquamated and degenerating cells but few leucocytes. There is some edema of the walls of the bronchi and the number of leucocytes is increased around the bronchi. The smaller bronchioles show a better preserved mucous membrane but many of the cells are vacuolated, presenting mucoid or hydropic degeneration, and desquamation is frequent. The *lung* shows practically the same picture as in the preceding; marked congestion and edema, small hemorrhages into the alveoli and emphysematous alveoli and dilated bronchioles. Many of the edematous areas show partial atelectasis. The apparently solid area from the right lung presents a more marked atelectasis and a greater degree of edema but no pneumonia. Other organs show marked congestion without other changes.

The microscopical picture in this case is similar to that in the preceding, but the changes are somewhat greater in intensity with a greater degree of necrosis and a well defined leucocyte reaction.

RABBIT 30.—Exposed thirty minutes to a concentration of 1:15,000. Killed four and one-quarter days after removal from the gassing chamber. Within five minutes after removal from the box the animal showed the first signs of irritation, rubbing its eyes and nose frequently. Six hours afterwards there was a well-developed conjunctivitis. By twenty-four hours the conjunctivitis had greatly increased with marked conjunctival edema, and the animal showed a marked bilateral coryza. By the second day the snuffles and coryza were much worse, the animal showing a marked respiratory wheezing, audible several feet away. The conjunctivitis had become distinctly purulent in character, with multiple subconjunctival pin-point hemorrhages, extreme edema and beginning corneal ulceration. Throughout the day the snuffles and wheezing greatly increased, the animal appeared sick, restless, with respirations greatly increased and shallow, these symptoms reaching their height in the evening of the second day. From the morning of the third day the respiratory symptoms gradually improved until the animal was killed, four and one-quarter days after gassing.

Autopsy.—The eyes showed a very severe purulent conjunctivitis with characteristic porcelain appearance of the cornea. The mucosa of upper respiratory tract showed marked congestion and edema and mucous exudate diminishing in intensity from the nostrils to the nasopharynx. In the anterior two centimeters of the nasal tract the exudate was purulent in character. The nasopharynx, larynx and trachea presented marked congestion of the mucosa, and the lumen of the trachea was filled with a frothy mucus extending into the bronchi. No hemorrhages or ulcerations were seen in the mucosa of the upper respiratory tract. Pleural cavities and pleuræ were negative. The lungs were uniformly markedly congested and apparently air-containing throughout. No pneumonic areas or hemorrhages could be felt or seen. The heart presented a marked right-sided dilatation. Beyond a marked congestion, other organs and tissues showed nothing.

Microscopic Findings.—Nose. Sections from the anterior nostrils show a marked necrosis and ulceration of the mucosa with a marked edema and congestion of the submucosa and a polynuclear infiltration. Great numbers of staphylococci are seen on the necrotic mucosa. Throughout the submucosa are numerous minute hemorrhages by diapedesis, and in one medium-sized blood vessel, a definite thrombus. The mucous glands of the nose and nasopharynx present intense mucoid change. Sections from the *pharynx* show the squamous epithelium to be intact for the greater part, but the outer half is necrotic, dry, looking like stratum corneum. *Larynx.* The surface epithelium is completely necrotic in many areas, particularly where a mucoid exudate lies upon the surface. In other areas it is preserved, but has lost its columnar appearance, and is reduced to a layer of pyknotic nuclei staining almost black with hematoxylin. In the mucoid exudate in the lumen there are great numbers of swollen desquamated mucoid epithelial cells and very few leucocytes. The submucosa is edematous, the edema, however, being very irregularly distributed. The blood vessels show marked congestion and the number of

leucocytes in the submucosa is not increased. The laryngeal mucous glands show marked mucoid degeneration. Many of the larger *bronchi* are filled with mucus. The columnar cells show marked mucoid degeneration and pyknosis. Practically every cell is converted into a goblet cell. There is no increase of leucocytes in or about the bronchi. The pulmonary vessels show extreme congestion and in many of these are large masses of fibrin, irregularly scattered through the red blood cells, or at times somewhat laminated, presenting the appearance of recent thrombosis. Throughout the *lung* atelectatic areas alternate with emphysematous. The alveolar spaces of the atelectatic areas show marked edema, being filled with a pink-staining finely granular precipitate. The bronchioles in these atelectatic areas are distended and are filled either with a similar edematous fluid or a more mucous fluid. No pneumonic areas are found and no large hemorrhages. Minute hemorrhages by diapedesis are found along the walls of the greatly distended capillaries. The other organs show nothing but intense congestion. (See Figs. 4 and 5.)

The lesions are practically the same as in Rabbit 33, except that they are more severe in the nose and mouth. The purulent character of the nasal lesions is probably to be explained by the development of a secondary infection due to a staphylococcus.

RABBIT 31.—Exposed thirty-five minutes to a concentration of 1:30,000. On removal from the gassing box the animal showed some irritation of the eyes and nose. Four hours after removal the animal had developed a well-marked conjunctivitis with erythema of the exposed skin surfaces, and beginning snuffles with scant nasal secretion. Within twenty-four hours there was marked increase of the conjunctivitis and coryza. The animal was killed thirty hours after gassing.

Autopsy.—Eyes showed a marked conjunctivitis with purulent exudate. Exposed skin surfaces showed erythema and edema. The mucosa of entire respiratory tract from nose to bronchi showed congestion, slight edema, and abundant mucous exudate. Pleural cavities negative. Pleuræ negative. Lungs presented uniform congestion without consolidation, the lung tissue being apparently air-containing throughout. No hemorrhage or atelectatic or pneumonic areas visible to the naked eye. The heart showed dilatation of the right side. In other organs nothing notable but congestion.

Microscopic Findings.—Nose. Squamous epithelium of the anterior nostrils shows patches of complete necrosis, these minute erosions or ulcerations being covered with a fibrinopurulent exudate. The remaining epithelium shows more or less pyknosis. There is very little edema of the submucosa and no small-celled infiltration or hemorrhages. On the skin side of the nostrils the edema is more marked than on the mucosal side, and there is marked necrosis, pyknosis and desquamation of the epidermis. *Pharynx.* Squamous epithelium of mouth and pharynx shows patches of pyknosis, contraction of the upper third with pyknosis of the nuclei resembling cornification, congestion of the blood vessels, and slight edema of the submucosa. *Larynx.* The columnar epithelium shows marked mucoid or hydropic degeneration. The majority of the cells of the upper layer are either vacuolated or are goblet cells. The nuclei stain very heavily, but the epithelium is for the greater part intact, without desquamation. In the lumen there is a thin albuminous fluid containing very few desquamated cells, leucocytes, no fibrin, and but a small amount of mucin. The submucosa shows a rather marked edema with the leucocytes slightly increased. The vessels are markedly congested. The mucous glands show increased mucus formation. *Trachea.* The epithelium is intact throughout the greater portion, but shows mucoid and hydropic degeneration. The lumen is filled with a thin mucoserous fluid. Well-marked edema of the submucosa with some increase in leucocytes. Marked congestion of the vessels. *Bronchi.* The lungs present practically the same appearance as in the previously described cases but with less edema and on the whole a less marked congestion. The bronchi contain a smaller amount of fluid. The epithelium is better preserved, although showing mucoid change and vacuolar change in the larger ones. There is very little atelectasis, the *lungs* being rather emphysematous throughout. There is no pneumonia and no hemorrhage. The other organs show chronic congestion, the liver a chronic coccidiosis with cirrhosis. (See Figs. 2 and 3.)

In this rabbit the lesions in the anterior nares are severe, the degree of necrosis there being comparable to that on the conjunctiva and cornea, but the laryngeal, tracheal and bronchial lesions are of the mildest degree.

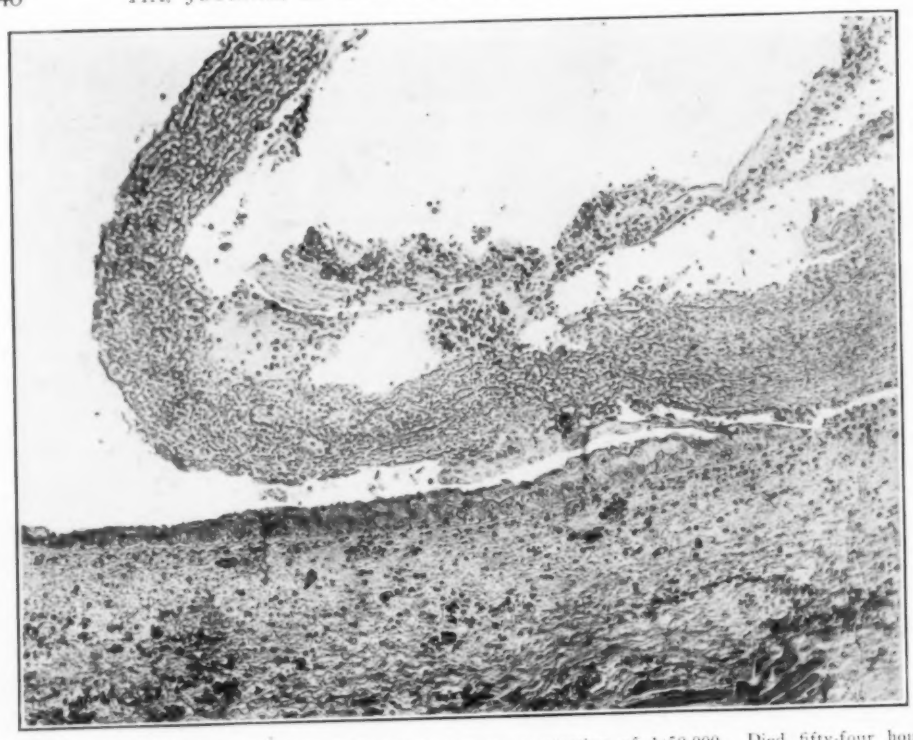

Fig. 8.—Rabbit 43. Exposed twelve hours to a concentration of 1:50,000. Died fifty-four hours after exposure. Section of tracheal wall, showing pseudomembrane in lumen and complete necrosis of the surface epithelium.

Fig. 9.—Section of large bronchus from same rabbit as preceding, showing diphtheritic necrosis of the mucosa. Early bronchopneumonia.

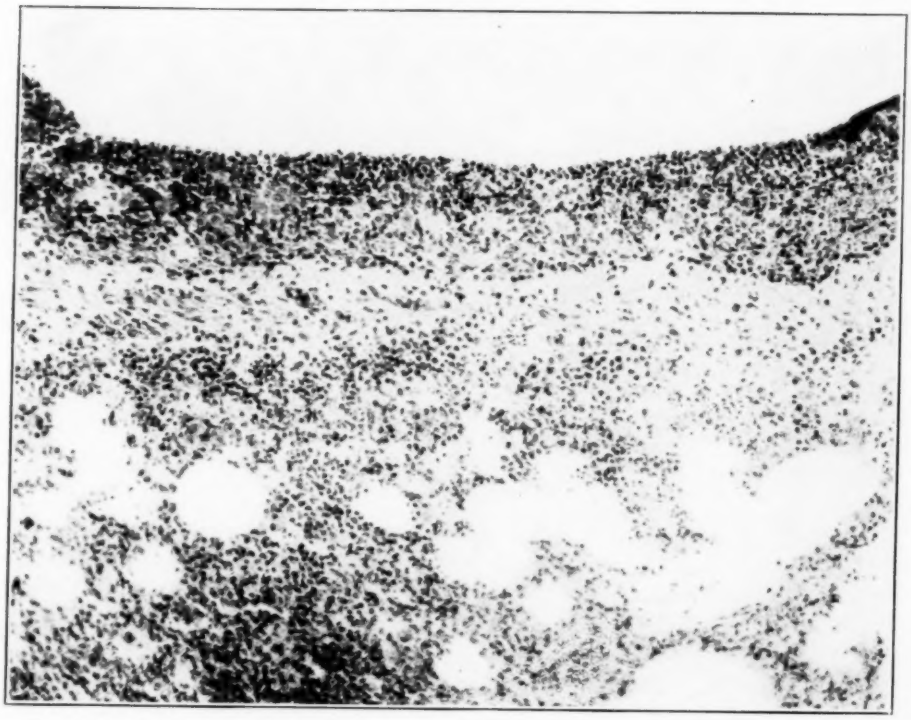

Fig. 10.—Rabbit 46. Exposed six hours to a concentration of 1:50,000. Died sixty hours after gassing. Section of large bronchus, showing purulent necrotic bronchitis.

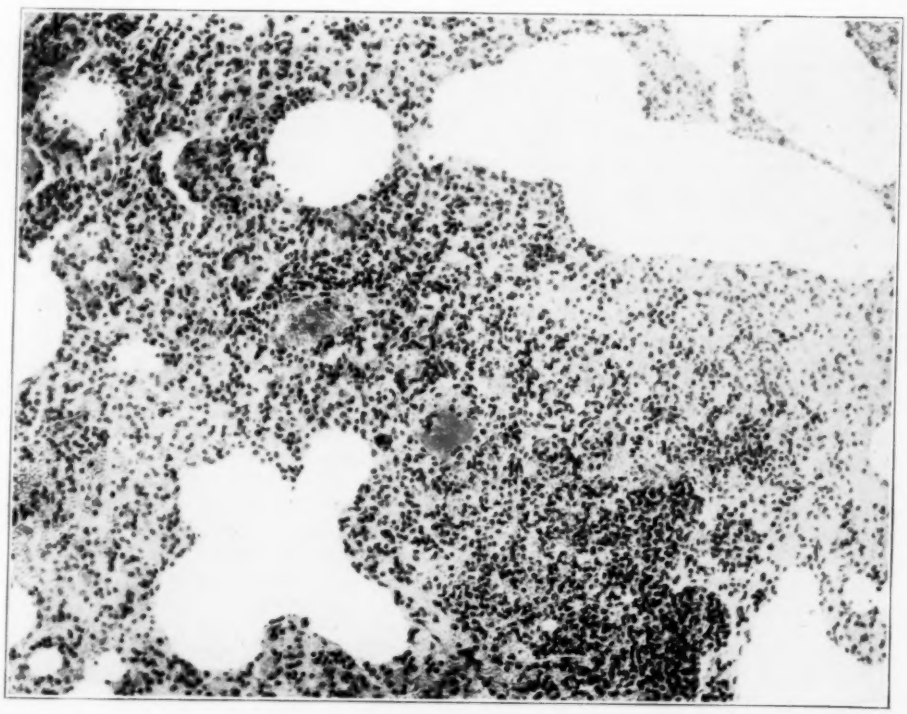

Fig. 11.—Section of lung from same case as preceding. Area of purulent bronchopneumonia with colony of cocci in the center of the field.

RABBIT 46.—Gassed six hours at a concentration of 1:50,000. Animal died sixty hours after removal from the gassing chamber. During the gassing the animal showed irritation within half an hour. At the end of an hour it became drowsy and was quiet with its eyes half closed. Within three hours there was a definite lacrimation and conjunctival edema, these conditions increasing during the remainder of the gassing. When taken from the box the eyes were very much congested, edematous and showed profuse lacrimation. By the next day the rabbit showed marked respiratory involvement, coughing all the time, and bubbling rales could be heard throughout its chest. These conditions increased during the next two days, the animal dying sixty hours after removal from the gassing chamber.

Autopsy.—Both eyes presented marked corneal opacity with mucupurulent conjunctivitis. Pharyngeal mucosa very markedly congested and edematous and covered with mucopurulent exudate. Buccal mucosa negative in appearance. Marked edema of all laryngeal structures and tracheal mucosa, the tracheal edema being most marked in the upper part, just beneath the larynx, where there were also small hemorrhages in the mucosa. Pleural cavities and pleuræ negative. Pericardial fluid increased, clear. Heart dilated; both sides filled with partly clotted blood. Both lungs were voluminous and air-containing without any airless areas except a small atelectatic area in the border of the lowest left lobe. On section the lungs showed moderate congestion and edema without any hemorrhages or pneumonic or atelectatic areas visible to the naked eye. Other organs showed no changes except congestion.

Microscopic Findings.—Nose. Anterior nares show a shrinking and pyknosis of the epithelium, the outer layers being desquamated and light staining, resembling cornified epithelium with pyknotic nuclei. In many areas this pyknosis and shrinking extends to the lowest layer of the epithelium. Through the lowest layer there are many hydropic cells and occasionally small vesicles are formed. The ciliated columnar epithelium shows a more marked necrosis, vacuolization and desquamation. There is marked edema of the submucosa extending to the cartilages and through the muscles. The mucous glands show extreme mucoid degeneration; the blood vessels, extreme congestion. There are minute hemorrhages about the mucous glands and the number of wandering cells is increased. The *buccal mucosa* and the *tongue* show necrosis of the upper half to two-thirds of the squamous epithelium, with partial desquamation of these dead cells in lamellæ. There is slight edema and moderate congestion of the subepithelial tissues. The mucosa of the *pharynx* shows the same changes with a more marked edema of the submucosa. *Larynx.* In the lumen, lying upon the surface, there is a fibrinopurulent membrane which is firmly attached in areas where the epithelium is completely lost. In these areas the picture is that of a diphtheritis. Colonies of staphylococci are present in the diphtheritic membranes and on the necrosed epithelium. Where the epithelium is preserved it shows marked vacuolation with hydropic and mucoid degeneration. In some areas the epithelium is still attached but is necrotic and infiltrated with polynuclears and eosinophile cells. There is a very marked subepithelial edema, extreme congestion of the blood vessels and areas of leucocyte infiltration, many of these being eosinophiles. This infiltration is most marked in the neighborhood of the diphtheritic areas. The cervical lymph nodes in this case show marked eosinophilia and great numbers of hemophages in the sinuses. *Trachea.* Mucosa of the trachea shows marked mucoid and hydropic degeneration. There is a diphtheritic necrosis, but the process is less marked than in the larynx. Edema and congestion of the wall are about the same. The epithelium of the larger *bronchi* shows marked degeneration and necrosis. There is an increase in leucocytes in the walls of the larger bronchi, the submucosa is edematous and the vessels are markedly congested. The majority of the smaller bronchioles contain a mucopurulent exudate and the bronchial wall is infiltrated with leucocytes. Around many of the bronchioles there are definite areas of a hemorrhagic purulent bronchopneumonia. Colonies of staphylococci are found in each of these areas. Between these areas the alveoli are overdistended and emphysematous. Other alveoli contain a heavy albuminous percipitate of edema. The *liver* presents a marked nutmeg liver, central necrosis and congestion of lobules. The *kidneys* show marked cloudy swelling and congestion. (See Figs. 10 and 11.)

The respiratory lesions in this animal are more pronounced than in any of the preceding, as is shown by the diphtheritic necroses in the larynx and trachea, the purulent bronchitis and bronchopneumonia. The cause of death

is considered to be an infective (staphylococcus) bronchopneumonia, secondary to the lesions produced by the gassing.

RABBIT 45.—This rabbit was gassed at the same time as Rabbit 46, in the same box for six hours at a concentration of 1:50,000. Its reaction during the gassing and afterwards appeared to be identical with that of No. 46, but the animal lived for seven days.

Autopsy.—The autopsy findings were the same as for No. 46, but the changes were more severe in character. The anterior nares showed extensive ulcers covered with diphtheritic membrane and the nasal cavity was filled with a mucoid fibrinopurulent membrane, this membrane extending through the nasopharynx and into the larynx and trachea. This membrane was in part firmly adherent to the wall, particularly along the posterior wall, while anteriorly it was loose and separated as a cast of the tracheal tube. Heart showed marked dilatation of both cavities. Pleuræ and pleural cavities negative. Large bronchi filled with purulent exudate. Lungs voluminous, markedly congested and edematous, with the picture of a diffuse bronchopneumonia.

Microscopic Findings.—The microscopic examination of the *nose*, *nasopharynx*, *larynx* and *trachea* reveals the presence of a diphtheritic inflammation with a membrane containing numerous colonies of cocci. This membrane is firmly attached wherever the epithelium is completely lost, but is loose and separates from the surface wherever the epithelium is still intact. In the larynx and trachea a large part of the columnar epithelium is replaced by a regenerating layer of large deeply staining pavement or cuboidal cells. The submucosa shows marked congestion, edema, scattered hemorrhages and leucocyte infiltration. The larger *bronchi* are filled with a fibrinopurulent membrane which is adherent to the wall and contains many large colonies of cocci. The epithelium is entirely absent except in a few places where there is a regenerating layer. *Lungs.* The lungs present the picture of an advanced fibrinopurulent bronchopneumonia with large areas of consolidation. All the bronchioles appear as abscesses. In some of these there are many large epithelial giant cells, syncytial in type, showing an attempt at regeneration, but the great majority show complete destruction of the epithelium. Syncytial epithelial giant cells are also found in some of the alveoli. Colonies of cocci are found everywhere. Many of the pneumonic areas show older and fresh hemorrhages and marked inflammatory edema. (See Figs. 12 to 20.)

This case presents a more marked diphtheritic inflammation of the upper respiratory tract and a diffuse purulent bronchopneumonia due to secondary infection following gassing.

RABBIT 43.—Exposed for twelve hours to a concentration of 1:50,000. Died fifty-four hours after removal from the gassing chamber. In the first stages of the gassing the animal showed nasal irritation, but later became drowsy and depressed, and sat with eyelids nearly closed. At the end of two hours increased lacrimation and conjunctival edema were first noted. When removed from the gassing chamber there was a well marked conjunctivitis with coryza and salivation. The animal would not eat or drink but appeared stupefied. The coryza gradually increased in intensity and within six hours after removal from the chamber bubbling respiratory sounds were heard over its thorax. Coryza and conjunctivitis increased during the first twenty-four hours, at which time there was a profuse seropurulent nasal discharge. The wheezing and bubbling respiratory sounds could be heard some distance from the cage. Respirations were rapid and apparently difficult. Thirty-six hours after gassing the rabbit was still much depressed and the respiratory sounds were louder. The animal frequently sneezed and coughed. There was a marked purulent discharge from the eyes and nose. Forty-eight hours after removal from the gassing chamber the animal was very weak, the respiratory movements more rapid and much forced, the thorax heaving. Both eyes were sealed with a thick purulent exudate. After increasing respiratory difficulty the animal died, fifty-four hours from the time of exposure.

Autopsy.—Marked purulent conjuctivitis with corneal ulceration. Erythema of the exposed portions of the skin. Marked edema of the subcutaneous tissue, particularly in the region of head, neck and thorax. Nose filled with purulent exudate, the mucosa showing deep necroses. Nasopharynx filled with mucopurulent fluid. Larynx and trachea filled with frothy exudate beneath which there was a membranous cast, partly adherent but decreasing in intensity downwards. The mucosa of the entire upper respiratory

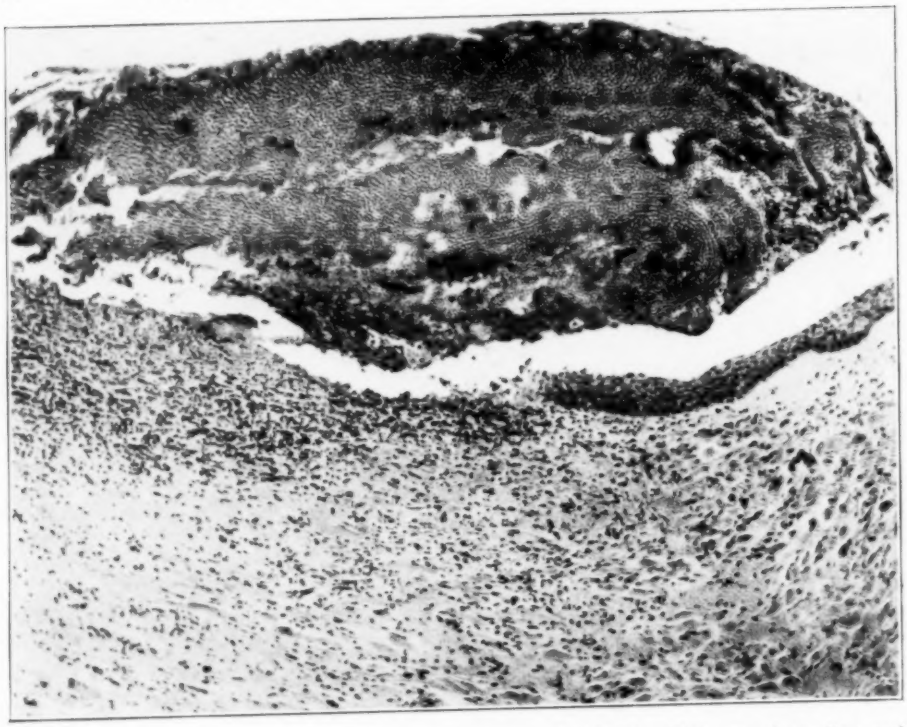

Fig. 12.—Rabbit 45. Exposed for six hours to a concentration of 1:50,000. Died seven days after gassing. Eschar from upper portion of larynx.

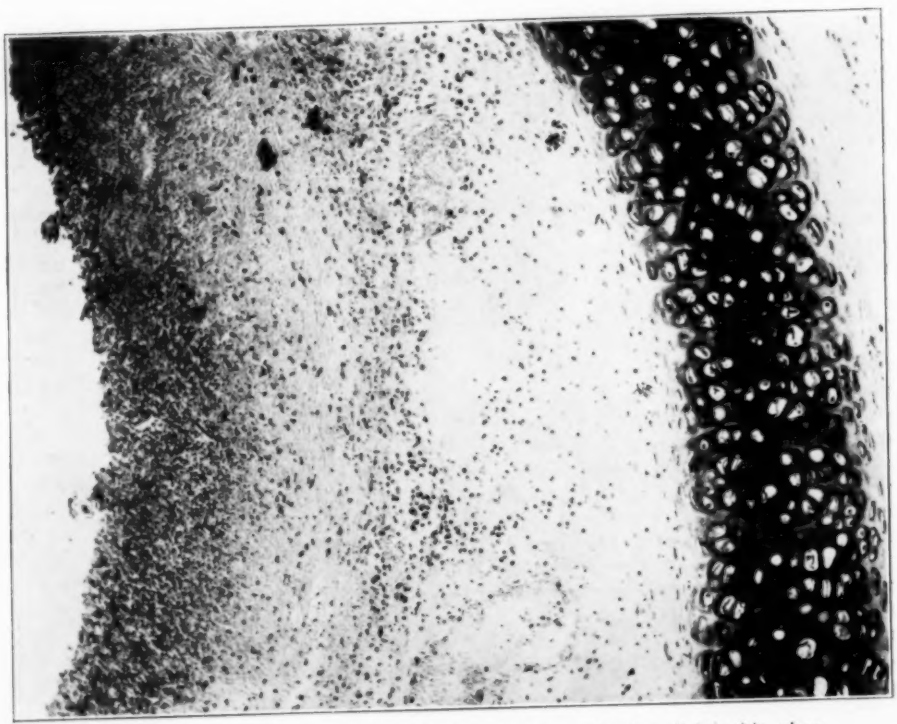

Fig. 13.—Same rabbit as preceding. Section of larynx showing diphtheritic ulcer.

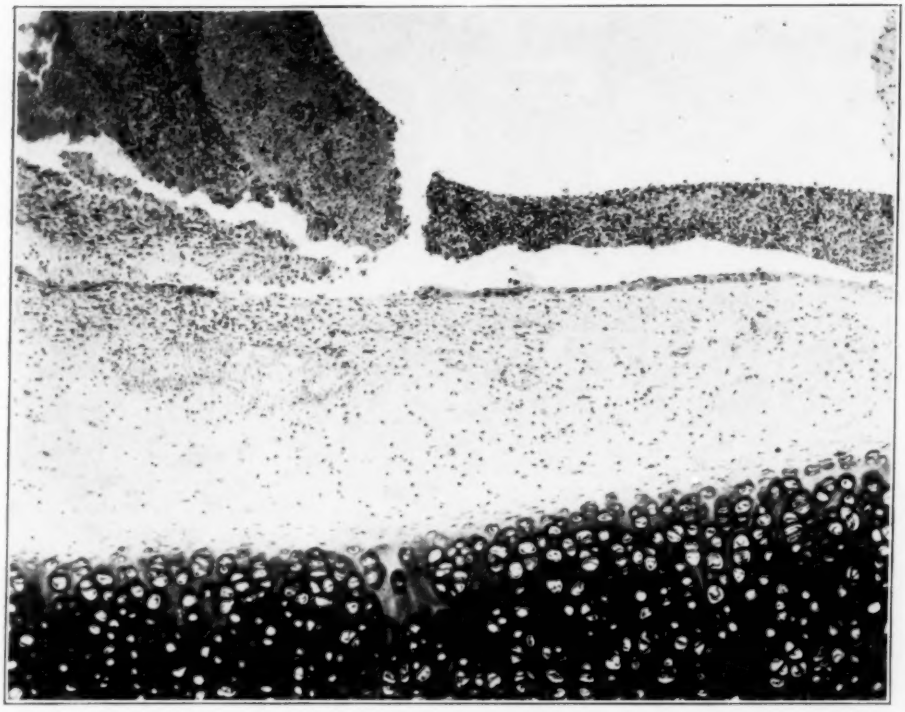

Fig. 14.—Same rabbit as preceding. Section of tracheal wall. Diphtheritic membrane. Epithelium in part gone and in part showing early regeneration. Congestion and edema of submucosa. Small-celled infiltration.

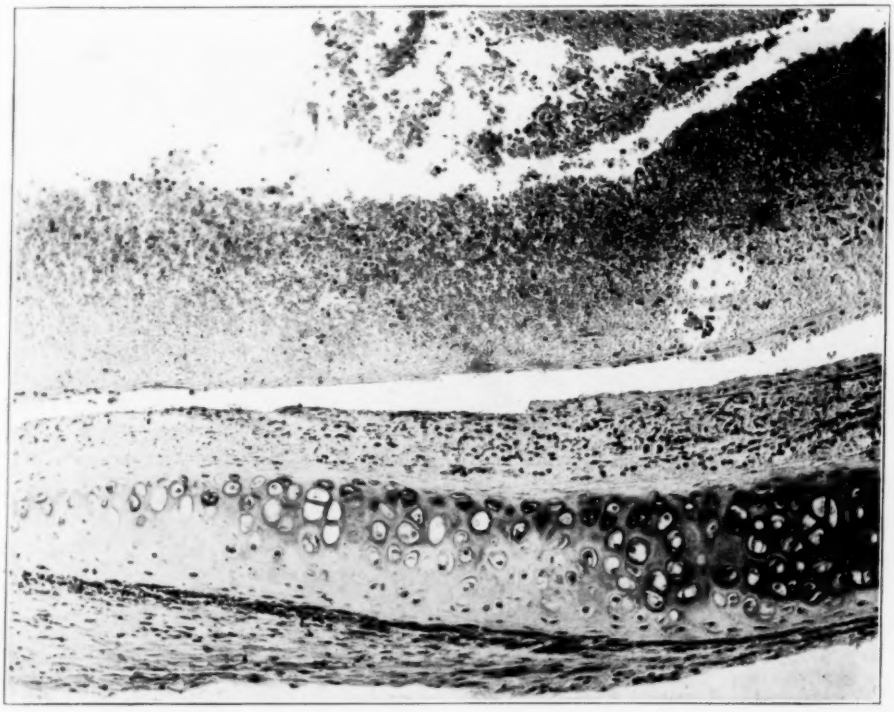

Fig. 15.—Same rabbit as preceding. Wall of large bronchus. Diphtheritic membrane. Complete necrosis of epithelium.

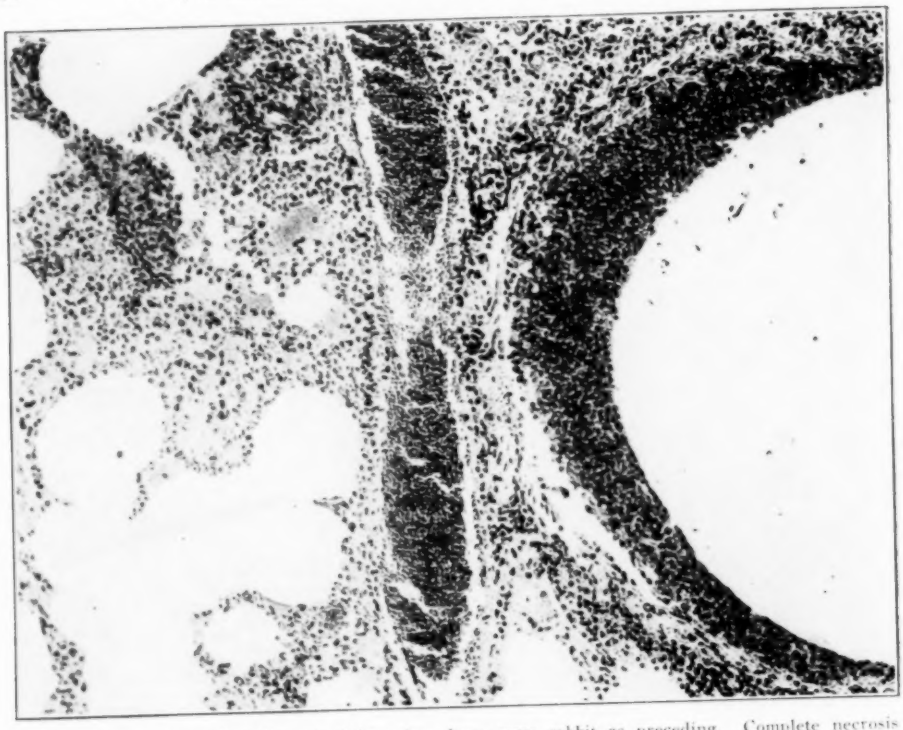

Fig. 16.—Section of medium-sized bronchus from same rabbit as preceding. Complete necrosis of bronchial epithelium; purulent exudate in bronchus. To the left of the congested vessel, colonies of staphylococci in the alveoli.

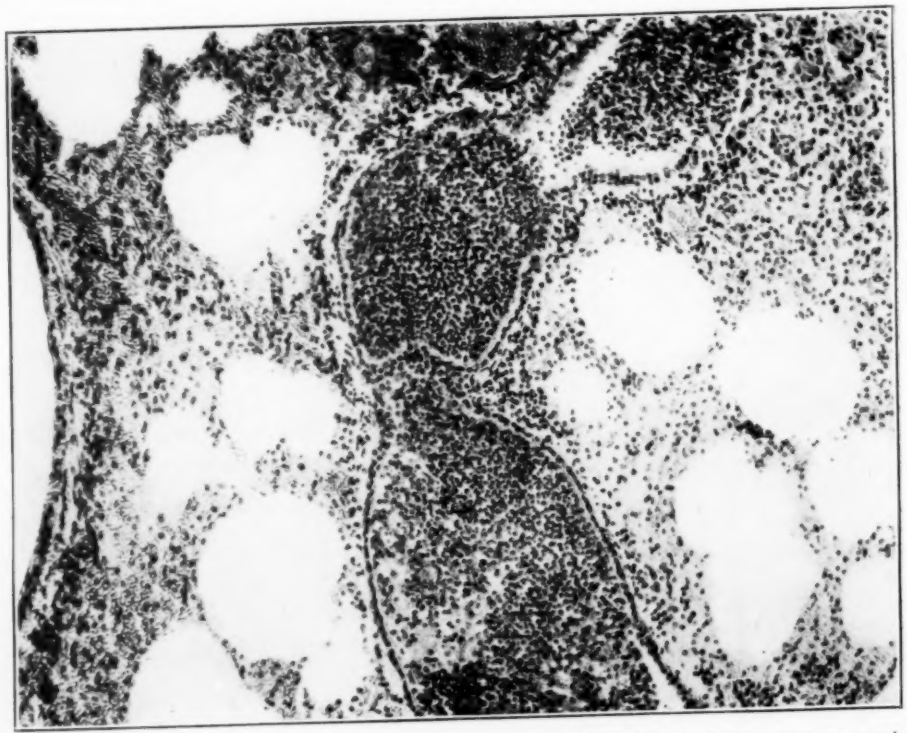

Fig. 17.—Section of lung from same case as preceding. Smaller bronchus filled with purulent exudate.

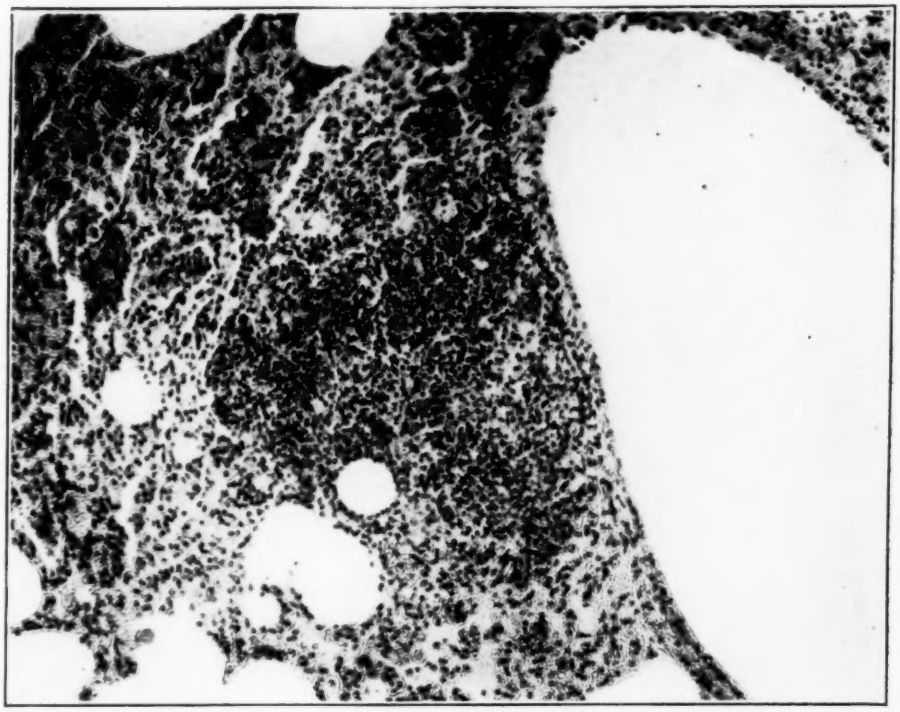

Fig. 18.—Section of lung from same case as preceding. Area of purulent bronchopneumonia with a dilated bronchiole showing necrotic epithelium.

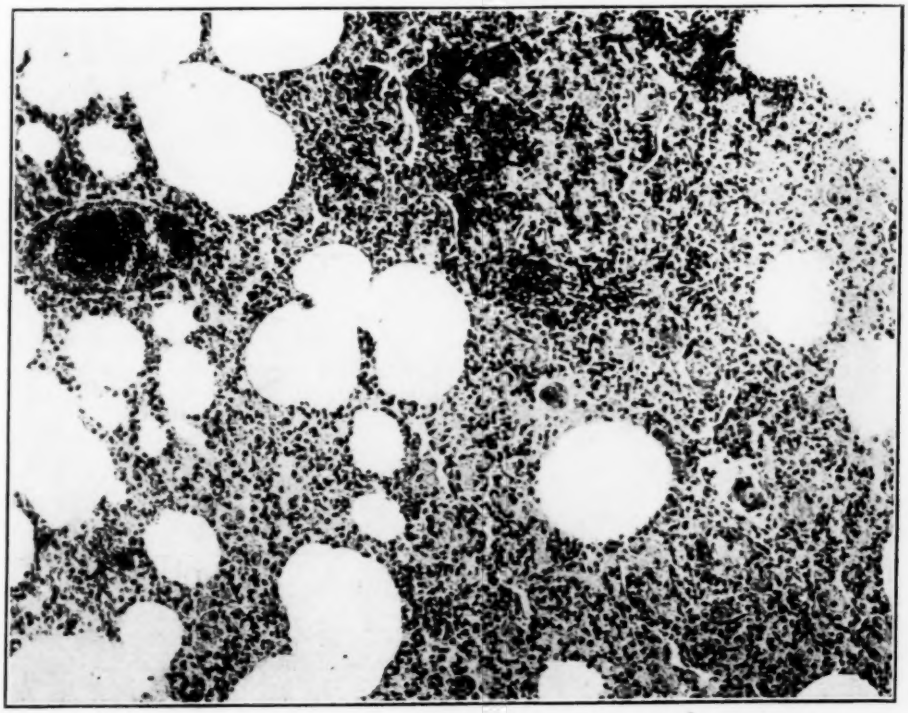

Fig. 19.—Section of lung from same case as preceding. Terminal bronchiole filled with pus and containing many regenerating epithelial cells. Large syncytial epithelial cells seen also in the neighboring pneumonic area.

tract was markedly congested and showed marked necrosis of the surface epithelium. The lungs showed marked congestion and edema. At the base of each lung there was an olive green area, the central portion of which was lighter in color. Bronchi filled with a thick mucopurulent exudate. Pleuræ were negative. Heart showed marked dilatation of the right ventricle. All other organs showed marked congestion. Some cloudy swelling in the kidneys. The external genitals were very erythematous and edematous.

Microscopic Findings.—The *nose* is filled with a diphtheritic fibrinopurulent exudate and the epithelium is completely necrosed, except for very small areas in the folds. The membrane is for the greater part adherent, but loosened in some areas. The submucosa shows marked congestion, leucocyte infiltration, and edema, extending into the muscles and cartilages. The mucosa of the *pharynx* shows a more marked necrosis of the squamous epithelium than in any of the above cases. The cells of the lowest layers are markedly pyknotic. The *larynx* and the *trachea* show a diphtheritic process, the surface being covered with a fibrinopurulent membrane which is firmly attached where the epithelium is entirely absent, but lying loosely on the surface where the epithelium is still intact or regenerating. In the membrane there are colonies of cocci. The epithelium of the larynx and trachea is reduced to a single layer of pyknotic nuclei over a large extent of surface. The submucosa shows marked fibroblastic proliferation, leucocyte infiltration and edema, with minute hemorrhages. The mucous glands of the larynx and trachea show some acini and ducts distended with mucus, but the greater number of the acini appear small, collapsed and pyknotic. The inflammatory infiltration and edema extend into the muscle. The mucosa of the upper part of the *esophagus* shows marked pyknosis and necrosis of the upper layers of the epithelium. The larger *bronchi* show a nearly complete necrosis of the epithelium and a fibrinous membrane adherent to the surface forming casts of the bronchial tubes. There is marked congestion of the wall and leucocyte infiltration of the surrounding tissues. The smaller bronchioles are filled with mucous and albuminous exudate with increased leucocytes. The epithelium is intact, but shows mucoid degeneration and pyknosis of the nuclei. A very few bronchi contain a mucopurulent exudate. The *lungs* show extreme congestion, numerous hemorrhages by diapedesis, a few small areas of early bronchopneumonia and atelectatic edematous areas beneath the pleura. The only bacteria found are those in the bronchioles containing the mucopurulent exudate. Marked congestion of all other organs. Cloudy swelling of the liver and kidney cells.

This case differs from the preceding in the severe diphtheritis of the upper respiratory tract with more marked evidences of healing in the larynx and trachea. It shows a severe secondary infective process of the larynx and trachea with less involvement of the bronchi and lungs.

RABBIT 44.—Gassed for twelve hours at a concentration of 1:50,000, at the same time with Rabbit 43. Reaction during the gassing identical. Developed a corresponding conjunctivitis and coryza with similar pulmonary symptoms. This animal, however, survived until 92 hours after the end of the exposure.

Autopsy.—Generalized mustard burn of the skin, especially where the hair was thin, in the form of a marked erythema, marked subcutaneous edema and dilatation of the superficial vessels. The untreated left eye showed a severe purulent conjunctivitis with corneal opacity and superficial ulceration. The right eye had been treated with dichloramine-T and showed a much less severe conjunctivitis and injury to the cornea. The upper respiratory tract was filled with frothy exudate. The mucosa, particularly of the trachea, showed a diphtheritic necrosis with membrane, most marked at the larynx and just below it, but extending into the bifurcation. Bronchi filled with frothy exudate. The lungs were voluminous, with marked congestion and very edematous on section. Atelectatic areas seemed to alternate with emphysematous. At the anterior border of the lowest lobe of the left lung, there was an area greenish gray in color, softened and apparently necrotic. Right ventricle and conus markedly dilated. All other organs congested. In the intestine, small necrotic areas, with inflammatory reaction about them, were found, the entire intestine being markedly congested.

Microscopic Findings.—Nose. Slough of the skin of the nose adherent. On the mucous membrane side an ulcer with slough adherent in some areas. Fibroblastic proliferation well developed. *Mouth.* Tongue shows numerous small areas of ulceration and sloughs extending down to the muscle. The remaining portion of the epithelium is intact but shows pyknosis and contraction of the outer half. *Pharyngeal* mucosa shows the same lesions.

Mucous glands of nose and nasopharynx show very marked mucoid degeneration. Intense congestion of the neighboring vessels. Patches of leucocyte infiltration. The *larynx* shows a purulent infiltration of the wall extending to the cartilages. A fibrinopurulent membrane is adherent to the surface over the greater portion and beneath the membrane there is a phlegmonous infiltration of the wall of the larynx. Small patches of epithelium upon the surface have the appearance of regenerating epithelium, regeneration taking place apparently from the ducts of the mucous glands. Numerous colonies of cocci are found in the pus. Below the larynx the epithelium is present over the greater part of the *tracheal* mucosa, which shows mucoid and hydropic degeneration. There are also islands of regenerated epithelium with some fibroblastic proliferation in the submucosa. The tracheal wall shows congestion, edema, small-celled infiltration and fibroblastic proliferation. The larger *bronchi* are filled with pus. Small diphtheritic areas are found on the mucosa, where the epithelium is entirely gone and the fibrinopurulent exudate is adherent. Walls of the bronchi are edematous, infiltrated with leucocytes, and the blood vessels are congested. Any epithelium remaining shows mucoid and hydropic degeneration. The *lungs* show extreme congestion and numerous small hemorrhages. The alveoli for the greater part are overdistended, emphysematous, although there are many small atelectatic areas in the neighborhood of plugged bronchi. The atelectatic areas show a marked edema. Practically all the bronchi and bronchioles are filled with a purulent exudate and around many there are areas of purulent bronchopneumonia. Colonies of cocci are found in the pus in the bronchi. Other organs show intense congestion. No other organs show changes, with the exception of stomach and intestine, in which small sloughs are found, probably the result of local action of mustard gas swallowed in food or saliva.

This rabbit shows a severe purulent and diphtheritic inflammation of the upper respiratory tract and a purulent bronchopneumonia, due to a staphylococcus, secondary to the more severe lesions caused by the gassing.

SUMMARY OF EXPERIMENTAL WORK

From repeated and carefully controlled animal experiments we have arrived at the following conclusions in regard to the production and nature of the respiratory lesions due to mustard gassing.

1. The respiratory lesions are proportionate to the concentration of mustard gas employed and to the length of exposure.

2. The mildest lesions are those produced by short exposures, such as ten to fifteen minutes, to dilutions of 1:110,000 or over; or very short exposures, one to several minutes, to higher concentrations.

3. Exposure to mustard gas causes almost immediate signs of nasal irritation on the part of the animal. It will almost immediately rub its nose and turn its back to the inflowing gas. Conjunctival symptoms, in the form of photophobia and increased lacrimation usually appear within two to three hours, the respiratory symptoms developing two to three hours later, as a rule, in the form of snuffles, increased nasal secretion or a more or less severe coryza. In the case of short exposure, or low concentration of the gas, the respiratory symptoms do not progress beyond a catarrhal stage.

4. In prolonged exposures, or exposures to higher concentrations, the respiratory symptoms appear at relatively the same time, but usually later than the conjunctivitis. They then increase in intensity for several days until a picture of diffuse diphtheritic inflammation of the respiratory tract is produced, as manifested by increasing difficulty in respiration, exudation, rales and coughing. The animal may die within forty-eight hours, or later.

5. The pathologic lesions in the mildest cases consist of a superficial de-

generation or necrosis of the epithelium of the mucous membrane, with congestion and edema and increased mucus secretion. These milder lesions are found chiefly in the anterior nares, the pharynx, larynx and upper portion of trachea; but animals killed after such exposures invariably show a more or less marked pulmonary congestion and edema, and increased bronchial secretion. From lesions of this degree, recovery, without secondary infection, usually takes place.

6. The severer lesions consist of deeper necrosis of the mucosa of the tract and the formation of a diphtheritic membrane in the anterior nares, nasopharynx, larynx, trachea and larger bronchi. The most severe lesions are always in the nares, pharynx, larynx and upper part of the trachea, the intensity decreasing toward the bronchi. The respiratory columnar epithelium suffers more than the epithelium of the mouth cavity, although irregular areas of complete necrosis of the latter may be produced. The entire epithelium of the larynx, trachea and larger bronchi may be killed outright and the surface covered with a diphtheritic membrane, which, for the greater part, is easily detached, forming a cast of the larynx, trachea and larger bronchi. The laryngeal and tracheal walls show edema, congestion and small-celled infiltration, but the edema is always less marked than in the case of the subcutaneous tissues or the conjunctivæ.

7. In the severe cases, secondary infection with staphylococci almost invariably occurs, and the lesions in the larynx, trachea and bronchi usually take on a purulent character within four to six days, if the animal lives that long.

8. In the mildest cases the lungs show congestion and edema with hydropic and mucoid degeneration of the epithelium of the bronchioles. In the more severe cases the necrosis of the epithelium extends into the smaller bronchial divisions and bronchioles and a secondary purulent bronchopneumonia, apparently usually due to staphylococci, follows. In these severer pulmonary lesions, atelectatic areas, due to the plugging of the bronchioles with exudate, usually alternate with emphysematous areas. The atelectatic areas are usually edematous or hemorrhagic. Secondary hemorrhage into the purulent bronchopneumonic areas is also frequent, in some cases the condition assuming the picture of a hemorrhagic bronchopneumonia. In the pneumonic areas following gassing, colonies of staphylococci are always present.

9. In the severe cases death may occur more quickly as the result of a diphtheritic or purulent laryngitis without the development of pneumonia, but in the majority of cases, the cause of death, so far as the respiratory tract is concerned, is the development of an infective purulent bronchopneumonia secondary to the injury produced by the gassing.

10. Cases with localized diphtheritic necroses in nose, mouth, larynx and trachea, without extensive bronchopneumonia, may recover with healing and cicatrization of these areas. Fibroblastic proliferation in such areas was noted as early as the fourth day after gassing. Cicatricial contractions of trachea or larynx may result from such healed lesions.

CLINICAL MATERIAL

The clinical features of mustard gas lesions of the respiratory tract in man were studied in the cases of seven soldiers who were severely gassed in the manufacture of mustard gas, although wearing gas masks. The concentration of the gas to which these men were exposed was so strong that all received severe burns, two of the cases terminating fatally. In addition to these severe cases, data were secured from 63 other workers with mustard gas who had had at one time or another milder respiratory symptoms following accidental exposure to mustard gas vapor.

CASE I.—Private Ha. Exposed one hour in several shifts. Within a few hours after the exposure he developed erythema of the skin, nausea and vomiting and complained of intense thirst. This patient developed no conjunctivitis, his eyes being sufficiently protected by the gas mask. Later, burns about the lips appeared and within the next few days, diphtheritic necroses developed over the dorsum of tongue, uvula, hard and soft palate, pillars of fauces, tonsils and pharynx. On the seventh day after the accident, large moist rales were present over both lungs, and he was thought to have a diffuse bronchopneumonia. The patient died eight days after gassing. The autopsy report of his respiratory tract changes will be found below.

CASE II.—Private S. Exposed three-quarters of an hour, in several shifts, to the same concentration as the preceding. During the next few hours, in addition to the development of conjunctivitis, nausea and vomiting and erythema of the skin, he complained of intense thirst, and later showed patches of diphtheritic necrosis on the lips, angles of mouth, hard and soft palate, uvula, pillars, tonsils, buccal surfaces, dorsum of tongue and gums. All of the mucous membrane of the mouth showed erythema and desquamation of the epithelium. When seen on the eighth day he could barely whisper and had physical signs of a diffuse bronchopneumonia. He died four weeks after the accident. Autopsy not permitted.

CASE III.—Private Mc. Exposed forty minutes in four shifts. Within a few hours after the exposure, coincidently with the nausea and vomiting and erythema of the skin, he complained of a very dry throat. For three days he had a hacking cough and complete aphonia. The roof of his mouth was very painful and on the third day one of the sore places in his throat "seemed to burst" and he coughed up membrane-like material, after which his symptoms were improved, but his voice remained husky and a bronchial cough persisted for some time. When examined eight days after the accident he had a catarrhal rhinitis and patches of diphtheritic necrosis over the mucous membrane of the mouth, particularly on the right pillar and in the posterior pharyngeal wall. Occasional loud moist rales were heard over his thorax. Respirations increased.

CASE IV.—Private W. Exposed one-half to three-quarters of an hour in two or three shifts. In the first few hours after the exposure he developed mouth and throat symptoms in the form of a dry sore throat and could barely whisper. When examined eight days after the accident he showed diphtheritic necrosis of the mucous membrane of the lips, angles of the mouth, hard and

soft palate, uvula, anterior and posterior pillars, tonsils and posterior pharyngeal wall. The roof of the mouth was covered with a grayish green diphtheritic membrane through which numerous discrete yellowish white elevations appeared, suggesting small pustules on erythematous bases. On the eighth day he developed symptoms of a diffuse bronchopneumonia from which he later recovered, after, in the meantime, having expectorated a fibrinous bronchial cast, containing streptococci.

CASE V.—Private M. Exposed one-half hour in one shift. Had severe thirst but no soreness of mouth or throat. He developed a temporary erythema of the mucosa of the hard palate with a small patch of diphtheritic necrosis. Voice husky, frequent cough and respiratory rate increased.

CASE VI.—Private E. Exposed ten minutes in one exposure. On the next day complained of a very dry throat. He showed only a temporary erythema of the mucous membrane over the hard palate. When seen eight days later his voice was husky, and he had an occasional dry cough.

CASE VII.—Private Hu. Exposed ten to twelve minutes in one shift. He developed a severe rhinitis and a sore throat, but showed only an erythema of the mucous membrane of the mouth. When seen eight days after the accident, his voice was still husky, and he had a laryngeal cough.

A large number of other cases of mild respiratory lesions were also seen. All of these were in cases with conjunctivitis. These patients complained usually of a dry or sore throat, huskiness of voice with or without an accompanying rhinitis. A dry laryngeal cough usually persisted for several days, a definite huskiness for a longer period. In two cases, short exposures to weak concentrations produced in susceptible individuals a fibrinopurulent rhinitis lasting several days. In the severe cases of mouth burns the most marked lesions were always on the hard and soft palate and the dorsum of the tongue. The mildest cases showed erythema of the same areas.

Respiratory Lesions as Seen at Autopsy

CASE I, PRIVATE HA.—

Nose.—Examination of anterior nares negative. No skin burns on nose.

Lips.—No burns of mucosa of lips.

Mouth and Neck Organs.—Tip of the tongue is negative. On the dorsum there are patches of grayish and grayish white coating beneath which the mucous membrane is desquamated. When the coating is removed there is a denuded reddened surface. These lesions increase in severity toward the root of the organ where they become diphtheritic in character and are covered with a greenish gray membrane. The tonsils and palatal arch show areas of diphtheritic necrosis covered with a grayish membrane. Mucosa of the palate is markedly edematous and presents elevated, reddened and grayish areas. The tonsils are about normal in size, with deep crypts. The right is negative on section. The left tonsil shows membranous patches and, on section, crypts containing fibrinous exudate. Mucosa of pharynx is covered with a thick, grayish, tenacious membrane, which, when pulled off, leaves a denuded, reddened surface. The epiglottis is covered with a thick, grayish mucus and the glottis

is filled with a similar mucus. Beneath this the mucosa is congested and shows small patches of superficial necrosis, but these lesions are less marked than in the pharynx. Below the glottis, the mucosa of the trachea is covered with a thick grayish mucus, beneath which the mucosa shows a congestion diminishing in intensity from above downward. There is no membrane in the trachea but in its lower portion and at the bifurcation there is a thick, grayish mucus in the lumen. The posterior wall of the trachea shows marked hypostasis but there is no visible necrosis of its mucosa. The esophagus shows congestion of its mucosa with superficial desquamation at the mouth but no changes below this.

Lungs.—There is no fluid in either pleural cavity. The lungs meet in the midline above the heart. Both lungs are free throughout. Pleural surfaces negative.

Left Lung.—There are delicate old adhesions between the upper and lower lobes. On the anterior surface of the lower lobe there is a small pigmented nodule beneath the pleura, a healed tubercle. There is no thickening or puckering of the pleura over the apex. Beneath the pleural surface there are numerous minute petechial hemorrhages which are larger and most abundant posteriorly. The lung is air-containing throughout. The upper lobe is voluminous and pink in color; the lower lobe shows marked hypostasis posteriorly. On section, the cut surface shows marked congestion and edema. Foamy fluid, thicker than the ordinary stasis edema, exudes abundantly from the cut surface. The lower lobe presents a marked hypostatic congestion. The small hemorrhages appear soft and fresh and the blood shows no discoloration. Small fresh agonal lardaceous clots are found in the larger pulmonary vessels, but no thrombi or emboli are visible to the naked eye. No pneumonic areas, no abscesses, no hemorrhagic infarctions and no airless areas are found. Anthracosis is moderate. The main bronchi are filled with a thick, frothy fluid which is rather viscous and is grayish white in color, but in the smaller branches becomes distinctly yellowish and thicker. Beneath this the mucosa of the bronchi is markedly congested.

Right Lung.—The right lung is very much heavier than the left and much deeper in color. There are delicate old adhesions between upper and middle, and middle and lower lobes. The lower lobe posteriorly is almost black in color, the middle lobe deep red, while the upper lobe is more pinkish. The subpleural hemorrhages are more marked in this lung than on the left side. The anterior margins of the lobes show emphysema. The greater part of the lower lobe shows a partial atelectasis and posteriorly a firm airless area almost black in color, about the size of a hen's egg. On section, there is extreme congestion and edema with areas of atelectasis throughout the lower lobe. Throughout the entire lung there are numerous firm, elevated, airless areas of small size, that are not wedge-shaped. The large airless area in the lower lobe is wedge-shaped with its base toward the surface, deep red, almost black in color and shows in its center a softer, lighter area, apparently around the blood vessel. No thrombi or emboli can be seen with the naked eye. The bronchi show the same fluid contents and changes in the mucosa as on the left.

Bronchial Nodes.—The bronchial nodes on both sides are rather small, soft, edematous and but slightly pigmented.

Microscopic Findings

Mouth.—Sections from the dorsum of the tongue show patches of diphtheritic necrosis and small ulcers from which the membrane has been loosened. The submucosa shows intense congestion, small-celled infiltration, some fibroblastic proliferation and numerous capillary thromboses. Some of the dilated vessels, either capillaries or lymphatics, are filled with coarse threads of fibrin without red blood cells and with only an occasional leucocyte. The mucous glands show intense mucoid degeneration with small-celled infiltration and many of the ducts are dilated and filled with mucus. Regeneration of the epithelium from the deepest portions of the folds and mouths of the mucous glands has begun. (See Fig. 20.)

Pharynx.—Sections of the pharyngeal wall show intact epithelium covered with a thick mucus. The submucosa shows marked congestion, edema and polynuclear infiltration with small areas of hemorrhage. There are numerous dilated capillaries or lymphatics filled with coarse threads of fibrin without red blood cells or leucocytes. The mucous glands show marked mucoid degeneration. The tonsils show marked congestion and edema. The greater part of the epithelium is intact, but there are localized patches of diphtheritic necrosis. There is an increase of the stroma and many sclerotic vessels.

Larynx.—Sections from larynx show a desquamative catarrhal laryngitis with small areas of diphtheritis (see Fig. 21). The epithelium is for the greater part necrotic, either entirely gone or represented by a single layer of nuclei. On the surface there is a thick mucofibrinous exudate forming a cast of the entire lumen and for the greater part separated from the necrotic surface. The submucosa shows congestion, edema and slight leucocyte infiltration.

Trachea.—The trachea presents the same condition as the larynx, a desquamative necrotic tracheitis with the formation of a thin mucofibrinous membrane over the surface.

Bronchi.—The larger bronchi are filled with a thick mucous exudate containing many desquamated cells, some polynuclear leucocytes and a few red blood cells, with little or no fibrin. The epithelium of the mucosa is in part intact, showing hydropic or mucoid degeneration, and in part desquamated. The bronchial walls show intense engorgement of the vessels, well marked edema and a moderate small-celled infiltration. The mucous glands show marked mucoid degeneration. The picture is that of a catarrhal desquamative bronchitis. (See Fig. 22.)

Lungs.—The lungs show extreme congestion and edema with numerous minute hemorrhages by diapedesis. Areas of emphysema and atelectasis alternate throughout the lung. The atelectatic areas show the most marked edema and are usually the areas in which hemorrhages are found. No pneumonic areas are found. The airless area in the lower right lobe is a recent hemorrhagic infarct, the central lighter portion being an artery obturated by a recent mixed thrombus. Other smaller recent hemorrhagic infarcts are found beneath

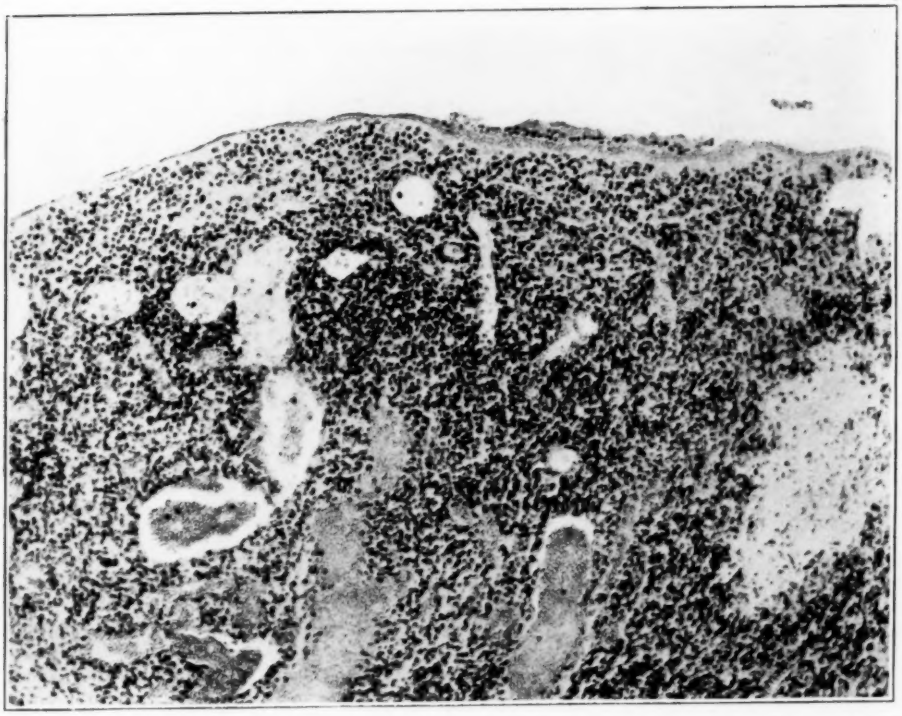

Fig. 20.—Case I. Private Ha. Mustard gas lesion of dorsum of tongue. Base of ulcer from which the diphtheritic membrane has become detached.

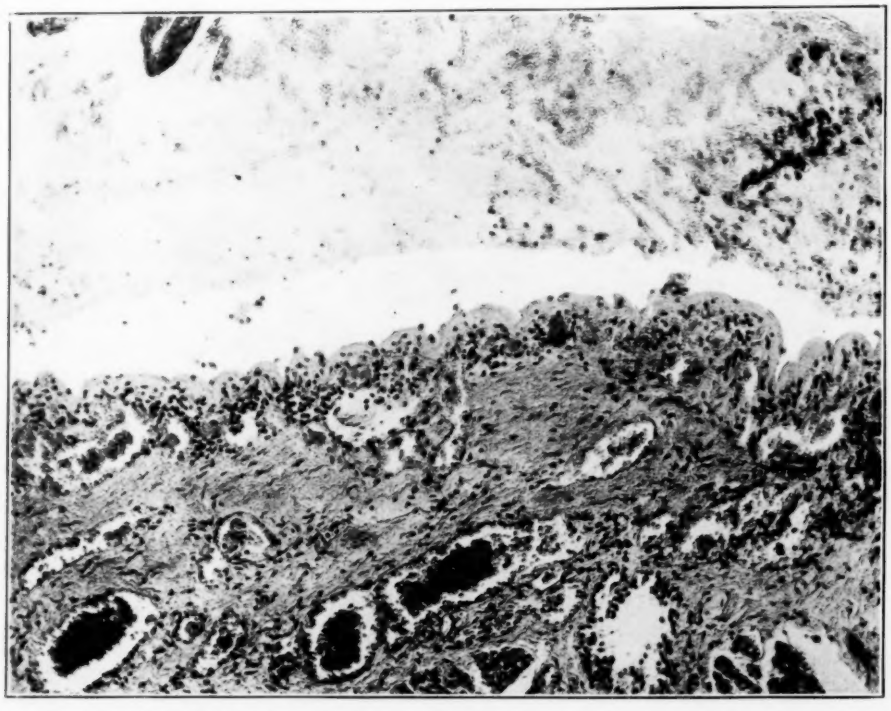

Fig. 21.—Case I, Private Ha. Section of diphtheritic lesion on vocal cord. Epithelium of mucosa completely destroyed and a mucofibrinous membrane partly detached from the surface. Extreme hyperemia of the vessels. Some small-celled infiltration.

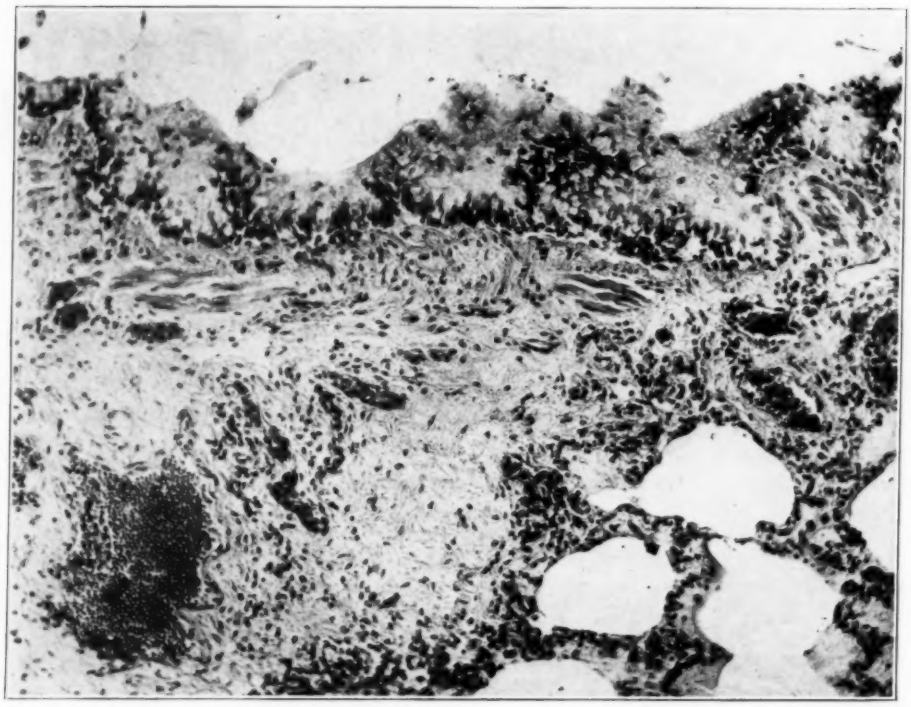

Fig. 22.—Case I, Private Ha. Section of main division of bronchus. Picture of catarrhal bronchitis. Marked mucoid degeneration and vacuolation of the bronchial epithelium. Congestion, small-celled infiltration, and edema of the bronchial wall.

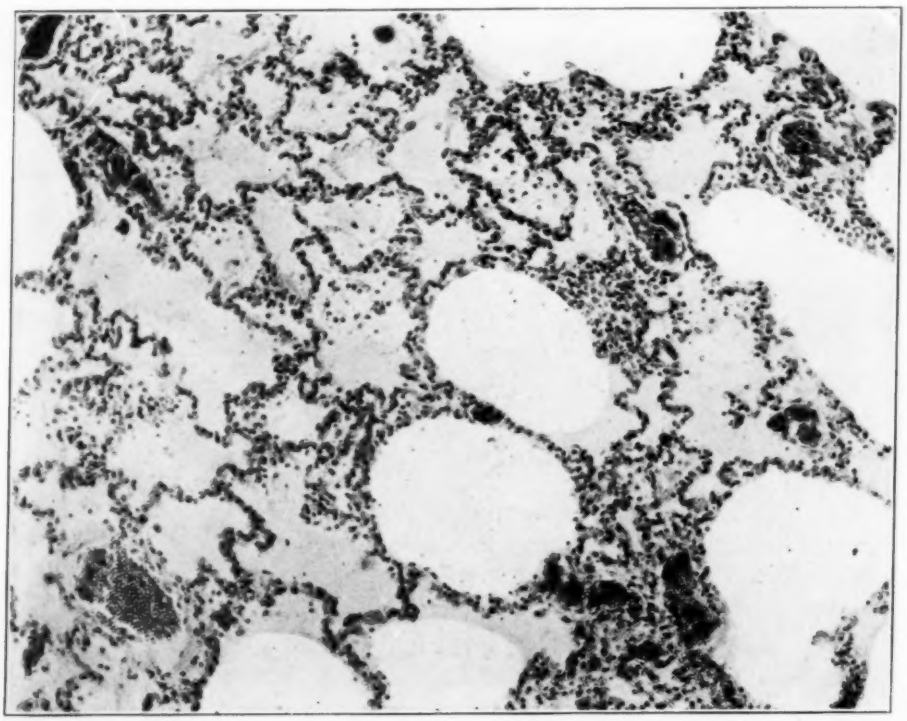

Fig. 23.—Case I, Private Ha. Section from upper lobe of lung. Congestion and edema. Acute emphysema.

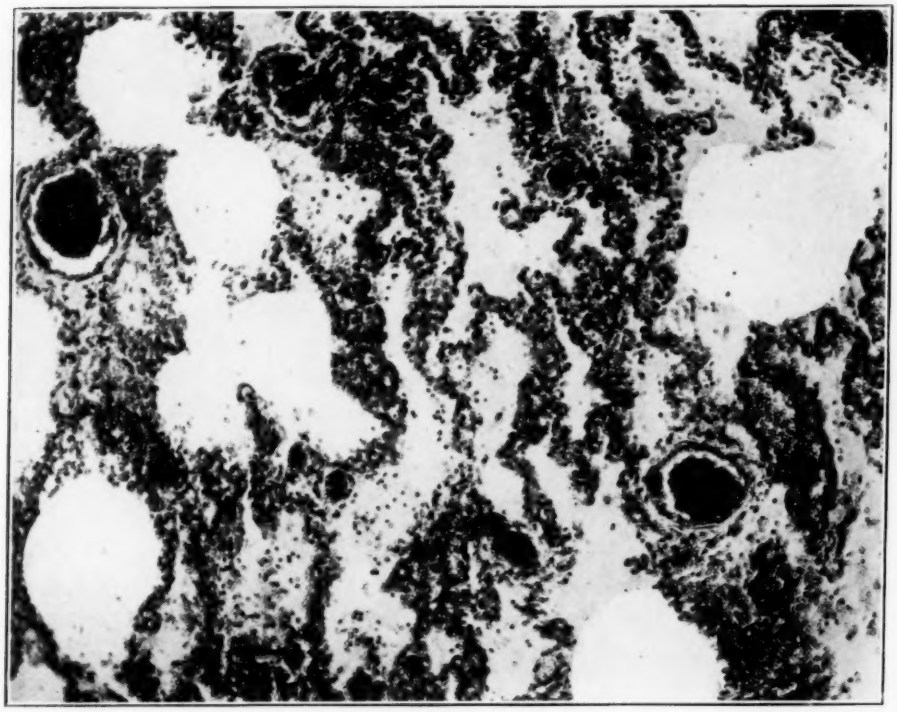

Fig. 24.—Case I, Private Ha. Section of lower lobe of lung. More intense congestion. Minute hemorrhages by diapedesis. Areas of partial atelectasis, alternating with emphysematous areas.

Fig. 25.—Case II, Private S. Mustard gas burns on lip, eight days after exposure.

the pleura of the right lung, with recent thrombi in the vessels leading to these areas. All the smaller bronchi and bronchioles are dilated and filled with a seromucoid fluid containing desquamated cells with some fibrin and occasional red cells. The epithelium of the smaller bronchi is intact for the greater part, but shows marked mucoid or hydropic degeneration. In many bronchioles desquamation of the epithelium has taken place. In no bronchi or bronchioles is there any purulent exudate. There are no old thrombi or emboli, and fat stains of frozen sections show no fat emboli. Smears of the bronchial exudate and from the cut surface of the lung show only occasional diplococci. (See Figs. 23 and 24.)

This case presents a marked degree of mustard gas degeneration and necrosis of the epithelium of the mouth cavity, larynx and trachea, decreasing in intensity to the larger bronchi and bronchial subdivisions, without infection or pneumonia. Death, in this case, probably resulted from shock and toxemia from the extensive areas of necrosed skin and secondary infection.

Summary of Clinical Observations

From the clinical cases coming under observation, mustard gas lesions of the respiratory tract in man are of the same nature as those produced experimentally in animals. In the milder cases there is an injury to the epithelium of the mucosa of the upper respiratory tract, particularly of the anterior nares, hard and soft palate, dorsum of tongue, pharynx, larynx and upper part of trachea. Rhinitis and laryngeal huskiness and cough with sore throat and thirst are the most common symptoms in individuals exposed to light and moderate concentrations. From these conditions recovery is usually prompt, but laryngeal huskiness and irritation may continue for some days or even weeks. No instances of secondary infection were observed in such cases.

In the more severe human cases, there is a greater degree of degeneration and necrosis of the epithelium of the respiratory tract, extending into the bronchi, but diminishing from the upper part of the trachea down, the most severe lesions being eschars on the palate, dorsum of tongue, pharynx and larynx. Associated with these, there is a widespread catarrhal tracheitis and bronchitis, with congestion and edema of the lungs. The one case autopsied showed no pneumonia. Under the conditions of warfare more severe exposures to mustard gas may produce diphtheritic lesions of larynx, trachea, and bronchi terminating in bronchopneumonia.

II. GASTROINTESTINAL LESIONS PRODUCED BY MUSTARD GAS

Practically no descriptions of gastrointestinal lesions produced by mustard gas exist in the literature. *Giraud* considered lesions of the digestive tract to be rare but thought that they might be caused by ingestion of food contaminated by the gas. In the clinical descriptions given in some of the army medical reports, as in the paper of *Mandel* and *Gibson* (*Journal American Medical*

Association, 1917, lxix, 1970-1971), epigastric distress, nausea and vomiting are frequent symptoms and appear in four to sixteen hours after gassing with mustard gas. *Pissarello* (*Giornale di Medicina Militare*, 1918, lxvii, 128-134) states that nausea and salivation are common symptoms in light cases and that vomiting, abdominal pain and diarrhea occur in the severe ones. These symptoms he considers reflex to the coughing. *Canelli* (*Rivista Ospedaliera*, 1918, viii, 2-6) gives the first published report of an autopsy on a case of mustard gas poisoning in which gastrointestinal lesions are described. He found the stomach distended with gas, the mucosa cloudy, glassy, congested in striæ, with numerous minute ulcerations along the major axis. Corresponding to the second flexure of colon there was a small, limited zone of subserous emphysema. The wall of the colon was thick, much congested and the mucosa was everywhere necrotic and covered with a sanious, purulent exudate. Corresponding to the second flexure of the sigmoid the necrosis extended into the submucosa and to the lowest strata of the wall. The duodenum showed a cloudy and congested mucosa, irregularly dotted with minute ulcers on a background similar to that of the stomach. The jejunum and ileum were nearly empty, anemic, semitransparent, with epithelium nearly uniformly desquamated. The esophagus and rectum showed no changes. In his macroscopic pathologic diagnosis, Canelli designates these conditions "acute gastroduodenitis with hemorrhagic erosions; acute desquamative enteritis, similar to the third stage of choleriform enteritis; severe diffuse hemorrhagic necrotic colitis." In his epicrisis he considers the acute inflammation of the colon to resemble macroscopically, in some particulars, both amebic and bacillary dysentery, although not clinically analogous, and considers that the gastrointestinal condition deserves special mention as indicating a selective action of yprite (mustard gas). He states further that in other reported necropsies upon cases dying from the action of other asphyxiating gases, without giving the references, chronic enteritis and gastrointestinal ulceration have been observed, and, therefore, concludes that there is a parallelism between the action of other toxic asphyxiative gases and mustard gas. *Karsner* noted in one autopsy case congestion of the stomach mucosa with submucous petechiæ in the fundus.

Other writers have hinted, without producing pathologic evidence, that the gastrointestinal symptoms are probably the result of mustard gas taken into the alimentary tract on contaminated food; but they may be due in many cases to shock or be secondary to the respiratory conditions.

EXPERIMENTAL

1. FEEDING.—Capsules containing .06-.24 c.c of dichlorethylsulphide were given to rabbits and guinea pigs in olive oil, butter and lard; similar capsules were given in meat to dogs. Animals were kept fasting, but were given water to drink. They were killed in series to get the complete pathologic picture from beginning to end of the process. For the purpose of brevity protocols are omitted, and the results of the experimental work are condensed as follows:

Symptoms.—These appear in 1-12 hours usually. Vomiting; irritation of

mucous membranes of mouth; profuse salivation; ultimately foul discharge from nose and mouth; foul diarrhea, at times tarry stools; depression; refusal of food and water. When allowed to live there is progressive anorexia, and weakness; by the sixth day the animals are so weak that they lie prostrate. Animal becomes greatly emaciated, with odor of foul putrefaction. Foul discharge from mouth persists. Death occurs usually by the 12th day, from .03-.06 c.c. doses, within three to five days from the .24 c.c. dose, for dogs, sooner for guinea pigs and rabbits.

Gross Pathology.—Delayed rigor mortis in animals not immediately autopsied. Emaciation. No free gas or fluid in peritoneal cavity. No general peritonitis. Liver congested; gall bladder dilated; spleen anemic, small and dry. Heart shows dilatation of right side. Peculiar chicken-fat clots in right ventricle of dogs. Lungs show varying degrees of congestion; no pneumonia. Kidneys congested. Chief lesions in gastrointestinal tract. Stomach and duodenum distended with gas and containing greenish or black fluid. Mucous membrane shows varying degrees of necrosis, localized in patches or extending over the entire surface. The necrosed areas appear greenish brown or gray, to black, without much inflammatory reaction. In the milder cases the mucosa may show marked congestion. Very little hemorrhage in stomach. Necrotic areas are usually thinned, but the animal usually dies before perforation occurs. Early peritonitis, over the thinned areas, occurs. Self-digestion by the stomach juices of the necrotic surface is delayed, from the inhibition of stomach secretions. Clean ulcers were not seen in the early cases, but were found in from six to twelve days, the ulcer extending into the muscle coat. The stomach lesions do not show the characteristic edema produced by dichlorethylsulphide in the skin and conjunctiva. A moderate edema was observed only in the cardiac end. The nonhemorrhagic character of the gastric lesions is also striking. Throughout the intestines there are patches of necrosis with congestion and slight hemorrhage, and more or less marked catarrh. Mesenteric glands swollen, edematous and congested. In the mouth, nose, pharynx, and esophagus of a certain proportion of the animals marked necrotic lesions, with secondary infection, occurred, as the result of local contact with the gas in swallowing or vomiting.

Microscopic Pathology.—Gastrointestinal mucosa shows varying stages and degrees of necrosis, involving the upper layers of the mucosa or extending through the submucosa into the muscle coats. In no case did the ulcer extend through the muscle. Preserved portions of the mucosa show dilated glands filled with granular or thready precipitate, or colloid masses, resembling hyaline casts. The epithelium of the deeper portions of the glands often shows a marked hydropic degeneration or liquefaction necrosis. There is usually little or no edema of the submucosa or tissues of the neighboring stomach wall. The eschar may be adherent to the surface, or the floor of the ulcer may consist of the muscle coats. These show polynuclear infiltration, congestion, some fibrinous exudate into the tissues, and occasionally hemorrhage. In the older cases there is often a marked small-celled infiltration of the muscle coats, extending to the subserosa, with fibroblastic proliferation of the latter and be-

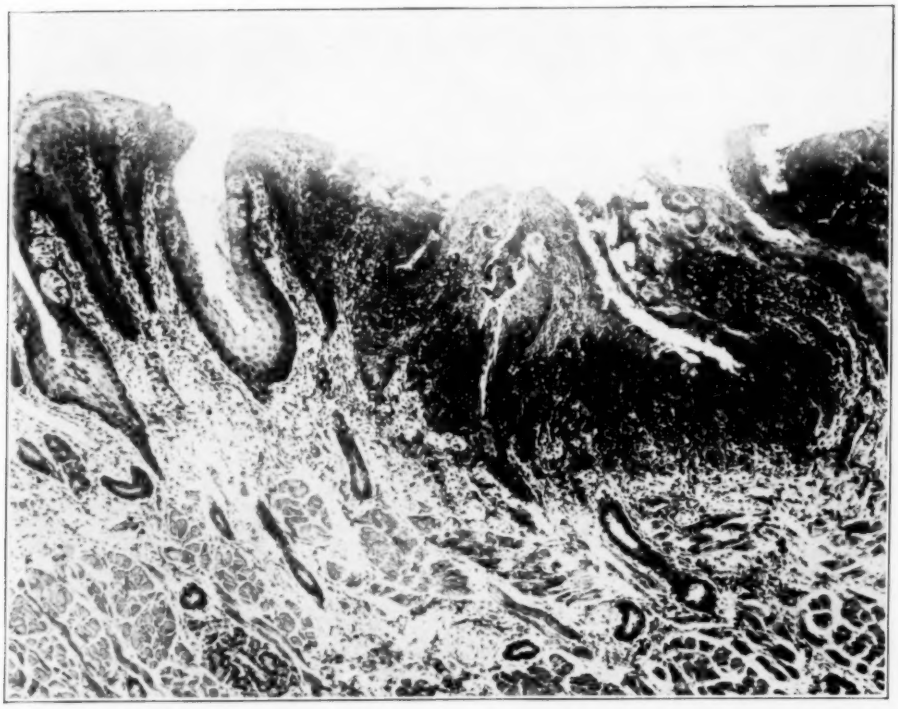

Fig. 26.—Rabbit 44. Exposed twelve hours to a concentration of 1:50,000. Died ninety-two hours after gassing. Mustard gas eschar on tongue.

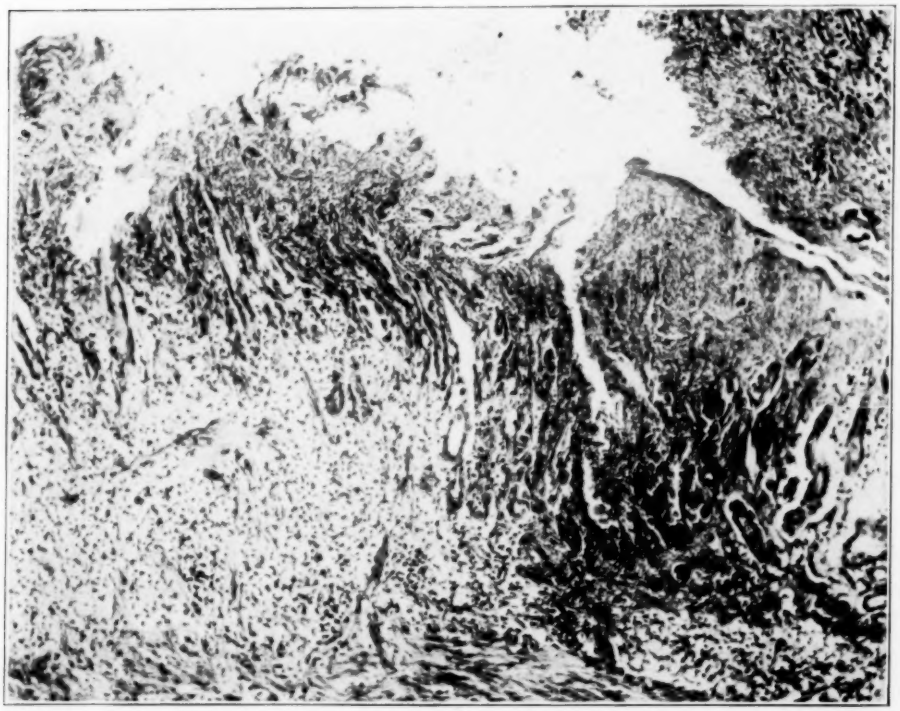

Fig. 27.—Dog 2. Received four minims of dichlorethylsulphide on meat. Died five days afterwards. Small mustard gas eschar in stomach mucosa. Early fibroblastic proliferation.

ginning peritonitis. The necrotic areas in the intestine are similar but show a more marked leucocyte infiltration, often extending to the serosa, but without any overlying peritonitis. The necrosis of the mucosa is most marked over the lymphoid tissue; Peyer's patches often being nearly completely necrosed. Numerous putrefactive bacteria are found in the necrotic areas of the mucosa. The entire mucosa is congested, and inflamed, showing occasional hemorrhages. The inflamed mucosa is but moderately edematous. There is marked mucoid degeneration of the epithelium. The mesentery is edematous, and shows at the insertion areas of inflammation. The mesenteric glands show sinus catarrh, and are congested. (See Figs. 27 and 28.)

2. Gastrointestinal Lesions in Gassed Animals.—In animals gassed

Fig. 28.—Dog 4. Received one minim of dichlorethylsulphide in capsule. Died twelve days later. Portion of base of very large eschar of stomach wall, extending nearly to the serosa. Marked leucocyte infiltration.

in the gassing chamber and not dying within several days there are found practically always a more or less severe congestion and catarrhal inflammation, which is more severe in the small intestine than in the stomach. In some cases, more severe lesions are found in the upper part of the digestive tract (diphtheritic necrosis, catarrhal inflammation, ulceration, etc.), but these can be explained as the result of gas swallowed with the air, saliva, or with food; and must be interpreted as direct local lesions. (See Fig. 26.) The generalized catarrhal condition of the small intestine may be explained by the assumption that dichlorethylsulphide or some substance resulting from it is excreted by the

intestine or through the bile or by the direct local action of minute quantities of mustard gas taken in with food or saliva and diffused throughout the gastrointestinal contents.

CLINICAL OBSERVATIONS

In the severe cases of mustard gassing seen by us, marked nausea and vomiting, gastrointestinal pain and diarrhea either preceded or were synchronous symptoms with the development of the cutaneous burns. We believe that these are reflex in nature and can be regarded as symptoms of the severe shock from which the patients suffered at this time. We also believe that the gastrointestinal symptoms seen in several patients after the symptoms of severe shock had disappeared were reflex and dependent upon the laryngotracheal-bronchial irritation (coughing).

In the fatal case the following gross appearances in the gastrointestinal tract were noted:

The *stomach* contains a small amount of thin, grayish fluid, slightly blood stained, and some milk curds. Throughout the entire mucosa there are numerous small petechial hemorrhages, these being most numerous toward the cardia where the mucosa is sprinkled with them, many of them being confluent. They all appear very fresh, the blood not being discolored and no erosions or ulcerations over them. The gastric mucosa is thin, smooth and soft, with early postmortem change. The *duodenum* contains a thin, grayish bile-stained fluid, the mucosa is congested and covered with a tenacious, thick, grayish mucus. Just below the pylorus there are numerous hemorrhages in the mucosa. The *small intestine* is distended with gas and at intervals there are small collections of thin fecal matter slightly bile stained. The mucosa is congested and there is marked hypostasis in portions of the loops without other changes. The *colon* contains gas and some formed fecal masses. The mucosa is negative.

Microscopic Findings.—The *stomach* shows a marked congestion of the vessels of the mucosa with numerous fresh hemorrhages. Postmortem digestion of the upper portion of the mucosa. The *duodenum* shows postmortem necrosis of the upper portion of the mucosa, congestion, and marked mucoid change in the glands of Brunner. The *small intestine* shows a postmortem desquamation of the surface epithelium, slight catarrh of the glands and congestion and edema of the mucosa. *Colon* shows a similar condition. *Appendix* shows evidences of old inflammation. No active process. The *mesenteric glands* show a marked sinus catarrh with many hemophages present in the sinuses.

It is hardly probable that the gastrointestinal changes observed in this case are the direct result of the mustard gassing. It is much more likely that they are entirely secondary phenomena.

(For the gastrointestinal lesions produced by subcutaneous and intravenous injections of mustard gas the reader is referred to the paper on "The General Pathology of Mustard Gas (Dichlorethylsulphide) Poisoning," *Journal of Laboratory and Clinical Medicine*, this number, p. 265).

CONCLUSIONS

I. RESPIRATORY TRACT

1. The action of dichlorethylsulphide mustard gas, upon the epithelium of the respiratory tract is escharotic in character, similar to its action upon the epidermis, cornea and conjunctival epithelium. Degeneration or complete necrosis of the epithelium, or deeper necroses extending into the submucosa, constitute the primary lesions produced in the respiratory tract by mustard gas in weak or strong concentrations. These lesions are most marked in the anterior nares, mouth, pharynx, larynx and upper part of trachea, diminishing in intensity toward the lungs. In the most severe cases, however, the bronchial epithelium may also undergo degeneration or necrosis. The subepithelial edema in the upper respiratory tract is not at all comparable in degree to that associated with mustard gas lesions of the skin and conjunctiva.

2. Following the primary lesion there develops a catarrhal or a diphtheritic rhinitis, localized stomatitis, pharyngitis, laryngitis, tracheitis or bronchitis.

3. In even the mildest cases there is marked congestion and edema of the lungs and catarrhal bronchitis. In the more severe cases the bronchitis may be diphtheritic in character. Secondary infection may occur, and, following the development of a purulent bronchitis, a purulent bronchopneumonia may result. We have observed no pneumonia resulting directly from the gassing. All of the pneumonias observed, following the gassing, have been the result of secondary infection.

II. GASTROINTESTINAL TRACT

1. Direct application of mustard gas to the mucosa of stomach or intestine, by means of contaminated food, produces localized degeneration, necrosis and ulceration similar in type to the lesions of the respiratory tract.

2. The mild catarrhal conditions and small localized eschars of the stomach and upper portion of the small intestine seen in animals gassed in the gassing chamber may be explained as the result of minute quantities of mustard gas swallowed with air or dissolved in the saliva.

3. The gastrointestinal symptoms seen in gassed human beings are probably chiefly reflex, either associated with shock or with the respiratory irritation. As in other forms of gassing, it is probable that erosions or ulcers of the stomach and intestine may be embolic in character, the emboli arising in the primary or infected mustard gas lesions of the skin or elsewhere. It is also possible that in man, as in the case of animals, localized eschars of the gastrointestinal mucosa may be produced by the direct action of mustard gas swallowed in contaminated food or saliva.

THE GENERAL PATHOLOGY OF MUSTARD GAS (DICHLORETHYL-SULPHIDE) POISONING*

By Aldred Scott Warthin, Ph.D., M.D., and Carl Vernon Weller, M.S., M.D., Ann Arbor, Mich.

Victor Meyer, the discoverer of dichlorethylsulphide, believed that mustard gas applied to the unbroken as well as to the scraped skin of rabbits could produce lesions in other parts not directly touched by the application (eyes and auditory canal). He also made a subcutaneous injection of two drops into the back of a rabbit. No effects were noted at the site of the injection, but the animal developed inflammation of both eyes, with severe snuffles, and died of pneumonia on the third day. From these data he concluded that the most severe action of dichlorethylsulphide develops only after its entrance into the blood. *Haldane* is reported as having confirmed Meyer's observation, by producing conjunctivitis and death from pneumonia through injection. *Kolls and Gilbert* have observed that 10 mg. of an alcoholic solution injected into the muscles and also intravenously caused only a temporary depression and loss of appetite with recovery in a week; but similar injections of 50-100 mg. in alcohol and water emulsion produced convulsions within one hour, and death in three hours.

The general trend of the clinical observations made by French and Italian medical men in field hospitals is to the effect that the lesions of mustard gas poisoning are local, and that no general toxic action is produced. *Giraud* makes the definite statement that all of the lesions observed by him were purely local. He only rarely saw general symptoms, rapid pulse and fever; and these symptoms he thought might be due to other causes than an intoxication. The frequent vomiting he considered dependent upon the respiratory irritation and attempts at coughing. *Mandel and Gibson* do not speak of any general toxic symptoms. *Pissarello* also considered the frequently occurring vomiting to be reflex to coughing. He concluded that ocular symptoms are due entirely to the direct action of mustard gas vapor; and that they are not produced by any substance in the blood of the gassed; and, further, carried out a series of experiments to show that there was no poisonous substance irritant to the conjunctivæ in the tears or sweat of soldiers suffering from mustard gas conjunctivitis. Since gastric symptoms, hemorrhage and ulceration, have been noted in other forms of gassing, notably with chlorine, some writers have assumed their analogous occurrence in mustard gas poisoning.

Canelli, in the first published Italian autopsy protocol of a mustard gas death, notes, in addition to the local lesions of skin and respiratory tract, a parenchymatous degeneration of the liver, fatty cloudy swelling of the kidneys, hemorrhage into adrenal medulla, acute gastroduodenalitis with hemorrhagic erosion, an acute desquamative enteritis, and severe diffuse hemorrhagic necrotic

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colitis. He seems inclined to the belief that the gastrointestinal lesions are analogous to those produced by other forms of gassing. *Mackenzie* in autopsies upon animals gassed with dichlorethylsulphide observed focal necroses in the liver, punctate hemorrhages in adrenal cortex, swelling and hyperemia of the gastroduodenal mucosa, and in one case hemorrhagic ulcerations near the pylorus. He could not, however, ascribe any positive relationship of these findings to the gassing. *McNee* observed acute hemorrhagic nephritis, degenerative changes in the central portion of liver lobules and minute hemorrhages in the brain, in a few instances. In the four mustard gas autopsies reported by *Karsner* the only pathologic findings, aside from the local lesions of skin and respiratory tract, were a dusky red congestion of all the viscera, including the brain in two cases, and submucous petechiæ in the fundus of the stomach.

The question of the internal pathology of gassing with mustard gas is, therefore, not yet satisfactorily answered; and the object of the investigations recorded in this paper has been to throw some light upon this problem.

I. GENERAL PATHOLOGY OF ANIMALS GIVEN LOCAL APPLICATIONS OF DICHLORETHYLSULPHIDE TO SKIN OR CONJUNCTIVA, OR EXPOSED TO ITS VAPOR IN GASSING CHAMBER

From observations made upon a large number of animals exposed to mustard gas, either by direct applications to the skin or eyes, or in the gassing chamber, the systemic symptoms shown consist of gastrointestinal disturbances, such as vomiting and diarrhea; disturbance of heart rate, usually an increased rate, but in severe cases the rate may be slowed; lowering of the temperature except with infection; decreased urinary elimination; in the blood a secondary anemia, leucocytosis or leucopenia; and nervous symptoms, as increased reflex excitability, tremors and convulsions, or marked depression, stupor and coma. The great majority of slightly or moderately gassed animals show no systemic phenomena. The most constant of the general symptoms are the gastrointestinal. While a certain number of cases showing these symptoms may be explained as resulting from slight quantities of mustard gas swallowed in the air or saliva, or on food particles, it is probable that the gastrointestinal symptoms are chiefly reflex to the respiratory irritation, or are a part of the general phenomena of shock. In all severe dichlorethylsulphide gassing an initial shock is very common, and the changes in temperature, circulation, etc., form part of the clinical picture of this condition. With the development of pneumonia or localized infection the usual systemic symptoms attending such processes are observable.

We have seen nothing to make us believe that Victor Meyer's idea, that the toxic action of mustard gas is exerted chiefly through the blood, is correct; indeed, all of our observations make us certain that local applications of mustard gas to the skin of distant parts can not produce conjunctivitis or local lesions at other sites. Meyer's conclusion was based upon an error in technic.

The insidious character of mustard gas, the difficulty in handling it, the ease by which invisible droplets, spray or vapor may be conveyed, and the frequent occurrence of such secondary transmitted lesions explainable in this way, are sufficient grounds in explanation of Meyer's incorrect judgment.

Likewise the pathologic findings in gassed animals give no convincing evidence of the absorption of mustard gas into the blood from the skin, eyes, or respiratory tract. The general pathology is as follows:

Central Nervous System.—Congestion; very rarely minute hemorrhages; in infected cases emboli are seen rarely.

Thyroid.—Congestion; no other changes, except as involved directly from the laryngeal lesions. This event is common enough in the severe cases of laryngeal and tracheal diphtheritis, when the thyroid is congested, edematous and infiltrated with leucocytes.

Heart.—Ventricles usually dilated. No changes observable in heart muscle.

Aorta.—Intima of great vessels occasionally shows fatty streaks.

Lung.—When not involved directly through the respiratory tract, as in local application to the skin, the lung shows congestion, with or without edema. In the case of infected skin or eye lesions pulmonary emboli, metastatic pneumonia, etc., may occur.

Spleen.—Congested. In some cases an increase in the number of pigmented phagocytes.

Adrenals.—Congestion. Occasionally minute hemorrhages in medulla. (These are probably postmortem.)

Kidneys.—Congestion. Frequently slight cloudy swelling. In infected cases more marked cloudy swelling, casts.

Pancreas.—Congestion.

Liver.—Marked congestion. In the majority of cases liver cells are normal; slight cloudy swelling and fatty changes are not rare, but their occurrence does not suggest any direct relationship with the gassing.

Gall Bladder.—A thinner, watery bile is usually present.

Gastrointestinal Tract.—Congestion and mucous catarrh are always present. Minute hemorrhages and erosions are frequently seen in stomach (vomiting?). Very rarely embolic hemorrhages and erosions occur, especially in animals with large eschars, or infected lesions. At times local eschars of the gastric mucosa occur; these are explainable as due to ingestion of contaminated food or saliva. The marked salivation seen in many animals and the swallowing of quantities of such saliva containing small amounts of mustard gas, offer a plausible explanation for the catarrhal conditions found in the gastrointestinal tract, without assuming, as some writers have done, that they are due to an excretion of mustard gas through the gastrointestinal mucosa. The intense splanchnic congestion usually present may also serve to explain the gastrointestinal conditions.

Mesenteric Lymph Nodes.—Congestion and edema.

Genital Organs.—No changes noted.

Urinary Bladder.—Negative.

II. GENERAL PATHOLOGY AS SHOWN IN HUMAN AUTOPSY

The protocol of the gross and microscopic general pathology of the one human autopsy case of fatal poisoning from mustard gas seen by us is given here in full, with the exception of the respiratory and gastrointestinal tracts, which are given in the preceding article.

AUTOPSY PROTOCOL.—*Private Ha.* Died 12:30 P.M., July 8, 1918.

(Autopsy by Dr. A. S. Warthin, 2:00 P.M., July 8, 1918.)

External Examination.—Young adult male body, length 170 cm., strong build, frame large, thorax deep, epigastric angle a right angle, abdomen on level with ribs. Musculature good, well developed. Panniculus abundant, particularly over abdomen and thighs. Hips rounded, slightly of feminine type. Neck thick, thyroid small, facies slightly suggestive of mouth breathing; general appearances of body suggest the lymphatic constitution. All regional lymph nodes prominent. Hair of head abundant, dull brownish in color, dry; scalp shows much dandruff. Face shaven, beard not heavy, body hair fairly abundant, pubic hair of feminine type. External genitals small, scrotum small, tight; testicles small; penis medium size, moderate phimosis. No anomalies. No deformities, defects or mutilations. No surgical wounds or scars.

Hypostasis.—Moderate postmortem hypostasis, pale in color, except over hyperemic areas. Superficial veins on upper portion of body contain but little blood.

Rigor Mortis.—Marked rigor mortis throughout body, except in right arm, where it has been broken by manipulation of the arm.

Body Heat.—Body is cold. (Cooled by undertaker.)

Odor.—Marked odor of gangrene over the skin, particularly from that of back.

Skin.—Marked pigmentation of skin of face, hands and forearms. Right hand shows irregular patches of pigmentation alternating with paler recent scars of older (mustard gas) burns. Hands show irregular patches, particularly between the fingers, of desquamation of the horny layer. No recent burns on hands.

Over the greater part of the body, from the collar line down to the boot line, the skin presents the appearance of a chemical burn, varying in degree from hyperemia, slight desquamation, dried blebs and bullæ, denuded areas, to areas of well-marked necrosis and eschar formation. These lesions are most severe in the axillary regions, inner aspect of arms, bends of elbows, flanks, genitals, thighs and back. Severe lesions completely encircle both thighs, particularly marked posteriorly where there is extreme necrosis, secondary infection and pus formation. The necrosis is very marked over the entire back, neck, shoulders and buttocks, where the skin is discolored, mottled red, grayish, yellowish gray, brown, black or greenish, with marked gangrenous odor. Deeper points of hyperemia corresponding to the hair follicles show in these discolored areas. Over a large part of these lesions the epidermis is desquamated in large bullæ, and the desquamated surface is brown, yellow or red. There are no large hemorrhages into these lesions, and very few petechial hemorrhages, the reddened areas being hyperemic only, the redness disappearing on pressure. From the discolored moist areas a cloudy foul-smelling serum exudes. This is not blood stained in any region. Through the hyperemic areas in many regions the hair follicles appear as opaque, yellowish miliary nodules. These are particularly marked over the scrotum.

The skin of the abdomen is hyperemic with a pale belted line corresponding to the protection afforded by belt worn by patient. This belted area of less injury disappears in the flanks and shows but slightly on the back. The anterior surfaces of the thighs are bright scarlet, marked hyperemia. The hyperemia stops rather abruptly over the legs about 15 cm. below the lower border of the patella. The lower portions of the legs show practically no involvement anteriorly; posteriorly there is slight discoloration and hyperemia (hypostasis?). The feet show no lesions.

The *face* shows no lesions except on the right side, around and below the right ear, where there is a slight desquamation of the epidermis, with some reddening of the edges and elevated portions of the lobe of the ear. Below the left ear there is slight desquamation without reddening. Over the *neck*, below the chin, are patches of dried vesicles, brownish red where the epidermis is desquamated, and red where it is still intact. The

hair shows no changes. On the *scalp* the only lesion found is an area of hyperemia above the right mastoid prominence. Here the scalp is scaly with a large amount of dandruff.

It is notable that the skin over the bony prominences, particularly over clavicles, scapulæ, etc., shows circumscribed patches of deeper eschar formation.

The areolæ of both nipples show strikingly the greater intensity of the injury around the hair follicles and sebaceous glands. Each nipple is surrounded by a deep zone of hyperemia in which the epidermis has been lost; through the hyperemic skin the yellowish, enlarged hair follicles can be seen.

The skin of *penis* and *scrotum* is discolored, necrotic and gives off a foul gangrenous odor. There is a well-marked phimosis, but the small portion of the glans exposed, around the meatus, is necrotic, yellowish and infiltrated with pus. A drop of pus exudes from the meatus. The remaining portion of the mucosa of the glans shows a marked inflammatory reaction (hyperemia, infiltration and edema). Through the discolored skin of the *scrotum* the yellowish necrotic enlarged hair follicles and sebaceous glands stand out prominently. Around the anus there is a zone of marked gangrene and suppuration of the skin.

The areas of skin (face, hands, legs and feet) not affected by the lesions show marked anemia.

Mucous Membranes.—These are pale, particularly the lips. They are dry but show no burns. Tip of the tongue shows no lesions. (See below.)

Eyes.—The cornea and conjunctivæ of both eyes are clear; there is no hyperemia, no discharge, no opacity. No signs at all of conjunctival involvement.

Nose.—Nasal openings negative.

Ears.—Auditory passages negative.

Edema.—Trace only about ankles; none in eyelids or below eyes. Over the burned areas the skin is swollen, tumefied, infiltrated, consistency increased, but pits only slightly on pressure.

MAIN SECTION

On section the panniculus is abundant, pale yellow, moist shining, and only slightly edematous. The superficial veins are markedly anemic. No free gas in *peritoneal cavity*. Abdominal recti deep red in color, with lighter patches of hyaline or Zenker's necrosis (as in typhoid). *Omentum* lies a handbreadth below the umbilicus, is very rich in fat; its vessels are empty.

There is no free fluid in the cavity. The *peritoneal surface* is clear, shining, rather dry, but shows no signs of inflammation. Upper coils of *small intestine* are distended with gas. *Cecum* is greatly distended, also *transverse colon*, and *descending colon* as far as the sigmoid.

Hepatic and *splenic* flexures collapsed.

Stomach in normal position, contains a small amount of fluid and gas. Vessels of stomach enormously congested. Pylorus is in normal position. Old adhesions around the *appendix*, but no active process. The appendix is 10 cm. long, patent throughout, and empty.

Lower border of *liver* in median line is three fingerbreadths below the ensiform, and about one fingerbreadth below costal margin in the right nipple line. The *spleen* is in normal position, the lower pole about two fingers above the costal margin.

The *diaphragm* on the left is in the 5th i.c.s., and at the 5th rib on the right.

The *thoracic muscles* are deep red, very dry and anemic.

The *costal cartilages* are white, and cut easily.

No free gas or air in the *pleural cavities.*

The *sternum* shows normal consistence, and its red marrow is in normal amount and appearance.

The *anterior mediastinal fat* is very abundant and shows numerous petechial hemorrhages. The fat is very abundant over the *pericardial sac,* and shows numerous petechial hemorrhages.

The *thymic fat* is abundant and contains numerous petechial hemorrhages. In it, the *thymus* is still present in the form of two distinct lobes, each of which is 5 cm. long and 3-5 mm. thick. Its color is pink, consistence firm; no hemorrhages in its substance.

The *lungs* meet in the middle line above the heart. The *apex* of the heart is in the 5th i.c.s., inside the left nipple line.

Both *lungs* are free throughout. There is no fluid in either pleural cavity.

Pericardium.—No gas in pericardial sac; fluid normal in amount, clear amber. Pericardial lining smooth, clear, moist, shining.

Heart.—Heart is small, smaller than cadaver's right fist; in marked rigor mortis, the left ventricle completely contracted, and the right one nearly so. The *auricles* and *venæ cavæ* are collapsed, nearly empty; on section contain but a small amount of dark fluid blood. The subepicardial fat is in excess; over the pulmonary artery, just above the conus, is a sclerotic patch ("soldier's spot") about the size of a dime; along the coronary branches, posteriorly over the left ventricle, are narrow stripes of sclerosis. There are numerous subepicardial hemorrhages, most marked in the neighborhood of the auriculoventricular groove. On section the heart contains a very little fluid blood and small thin lardaceous agonal clots, particularly in the right ventricle, extending into the pulmonary artery.

The *mitral* opening admits two fingers; the flaps are negative. In the left auricle a small agonal lardaceous clot. The left ventricle wall measures 20 mm. in thickness, the *muscle* is deep brownish red, firm, and shows no cloudiness, fibroid patches or fatty change. No fatty change seen beneath the endocardium.

The *tricuspid* opening admits three fingers barely. Its flaps are normal. Small agonal clot in right auricle. The *foramen ovale* is patent, an oval slit admitting probe 3 mm. in diameter, but well guarded by membranous curtain. The *pulmonary artery* admits two fingers, the pulmonary semilunar valves are negative. The *right ventricle* wall measures 3-8 mm. in thickness, about one-half of this being fat tissue. The *aortic opening* admits the thumb easily. Its semilunar flaps negative. The beginning of the aorta shows very fine stripes and patches of fatty degeneration of the intima. Arch of aorta negative; also its main branches. Pulmonary artery and main branches empty and negative.

(For protocol of lungs, see paper on Respiratory Lesions.)

Examination of *thoracic duct* negative.

Thoracic aorta shows linear stripes of fatty degeneration.

(For protocol of mouth and neck organs, see paper on Respiratory Lesions.)

The cervical *esophagus* shows some injection of its mucosa at its mouth with superficial desquamation; below this no changes except postmortem hypostasis. A small amount of stomach contents in the lower portion.

The *thyroid* is small; but on section shows normal amount of colloid.

Parathyroids, four in number, brownish in color, about normal size.

Cervical nodes are about normal in size, some larger, translucent, slightly edematous.

Parotid and submaxillary glands are normal in size and appearances.

Great vessels and nerves of neck region are negative.

Abdominal Organs.—The *spleen* is somewhat enlarged, soft, flattens on the board, its capsule slightly wrinkled. On its surface are the remains of a few old adhesions to the diaphragm. On section the pulp is soft, deep brownish red, rises above the trabeculæ, the cut surface slightly shagreened. Bleeds rather poorly. Follicles barely visible. There are no infarcts, abscesses, or other lesions apparent.

The *adrenals* are surrounded by abundant fat tissue. Both are normal in proportion, the cortex pale yellow and somewhat fatty, the medullary portions showing no postmortem changes. No pathologic changes apparent.

The *kidneys* have large fatty capsules. Fibrous capsules strip very easily. Both kidneys somewhat enlarged, plump and markedly congested. Surfaces smooth, veins congested. On section both kidneys bleed freely. The cut surface shows extreme congestion; the outlines between labyrinths and medullary rays are not distinct. The surface is slightly cloudy (slight or moderate cloudy swelling). The pelvis of the left kidney is negative; that of the right is dilated, filled with cloudy urine, and its mucosa slightly injected.

The left *ureter* is normal in size and appearances; the right is dilated with cloudy urine.

The *urinary bladder* is moderately distended, containing about 60 to 70 c.c. of turbid urine. Mucosa is pale, negative.

The *prostate* is of normal size and shape; on section normal in appearance.

The *seminal vesicles* contain a small amount of thin brownish semen on the right side; on the left they are nearly empty; and the walls show some thickening.

The *testes* show congested tunics. No fluid in sacs. On section both organs are rather small, slightly congested and slightly edematous. The left testis shows slight fibrosis extending from the rete.

(For protocol on gastrointestinal lesions, see preceding article.)

The *liver* is much enlarged, particularly the right lobe; but the lower border is rather sharp. Capsule negative. Surface smooth. Color deep brownish red with paler anemic

areas. On section bleeds very freely. Consistency fairly firm. Cut surface uniform deep reddish brown, the lobules enlarged, with congested central areas and slightly cloudy parenchyma (slight cloudy swelling). Anemic areas show slight fatty shine.

The *bile passages* are patent. Gall bladder small, contains a moderate amount of thick brownish bile, no concretions.

The *portal vein, common duct* and *inferior vena cava* negative on section.

The entire *splanchnic area* is congested.

The *retroperitoneal* and *mesenteric* lymph nodes are enlarged, markedly congested and somewhat edematous. The prevertebral *hemolymph nodes* are hyperplastic, deep red, and very numerous.

The *thoracic* and *abdominal aorta* small in size (hypoplastic), empty; the intima shows linear stripes of fatty degeneration, most marked in the neighborhood of the coeliac axis.

Semilunar ganglia and *solar plexus* negative.

NERVOUS SYSTEM.—*Head.*—The *scalp* is negative except for changes mentioned above. Periosteum of cranium negative. In the right parietal bone a circular area of slight hyperostosis resulting from a cephalhematoma at birth. Corresponding to this area of elevation, there is on the inner surface of the *skull cap* a marked pacchionian depression almost perforating the greatly thinned outer table. The skull cap is thin; dura adherent all over; the meningeal grooves and pacchionian depressions unusually marked for age of cadaver; the lamina vitrea rough and dull; the dura is thickened throughout. The arachnoid shows numerous focal thickenings; the subarachnoidal fluid is markedly increased (edema); no evidences of inflammation. *Central longitudinal sinus* is negative. The *basal meninges* are slightly thickened and unusually tough.

The *basal vessels* are negative.

The entire *leptomeninges* are somewhat thickened, but strip easily.

The *cerebral convolutions* are rather sharp, but show no focal lesions. The ventricles are somewhat dilated; the cerebrospinal fluid is increased greatly, but is clear. The *ependyma* is normal.

The *chorioid plexus* is markedly congested on both sides. The *pineal* gland is normal in size and appearance. On section the *cerebrum* shows congestion and edema. No hemorrhages found.

The *cerebellum* shows marked congestion and edema. Dentate nuclei are normal. No lesions in cerebellar lobes. The *basal ganglia, internal* and *external capsules* are negative.

The *pons* and *medulla* are congested and edematous. No lesions apparent.

The *cervical cord* shows slight congestion and edema. No lesions seen.

The *hypophysis* is of normal size, congested.

Basal sinuses congested. Base of skull negative.

PROVISIONAL GROSS PATHOLOGIC DIAGNOSIS.—"Mustard gas" burns of skin and upper respiratory tract; gangrene and secondary infection of skin; shock; toxemia; edema, congestion and early hemorrhagic bronchopneumonia. Passive congestion of all organs. Splanchnic congestion marked. Moderate parenchymatous degeneration of kidneys and liver (toxic); multiple petechial hemorrhages; congestion and edema of brain and cord; thymicolymphatic constitution.

MICROSCOPIC FINDINGS

Cerebrum.—Sections taken from all parts of the cerebral cortex, basal ganglia, floor of ventricles, internal capsule, show intense congestion, edema and a few minute perivascular hemorrhages.

Pons, Medulla and *Cerebellum.*—Show a similar congestion and edema.

Meninges.—Old thickenings. No active process. Marked congestion of the vessels and edema. In the larger pial veins there are agonal clots rich in leucocytes.

Hypophysis.—Intense congestion, otherwise negative.

Pineal Gland.—Large calcareous concretion. Gland substance smaller in amount than normal. Marked edema.

Spinal Cord.—Edema. Congestion. Postmortem myelinosis.

Heart.—Subepicardial fat abundant. Vessels congested. Numerous petechial hemorrhages throughout the fat. Heart muscle fibers somewhat smaller than normal—an acute simple atrophy. Stroma somewhat increased around the coronaries in the left ventricle wall. Endocardium is negative. Heart muscle shows very slight parenchymatous degeneration. No fat. Mixed agonal clots taken from the heart show white clot with very few leucocytes while in the red portions of the clot there are large collections of leucocytes.

Aorta.—Stripes of marked fatty degeneration in the intima. These are longitudinal

and stain rather brownish red with sudan III and also a brownish red with scharlach R. Osmic acid not successful.

(For respiratory tract and neck organs, see preceding article.)

Thyroid.—Vessels congested. Otherwise negative.

Cervical Lymph Nodes.—Show marked sinus catarrh with numerous hemophages in the sinuses. The *cervical hemolymph nodes* show marked congestion and hemolysis, many hemophages in the sinuses.

Thymus.—Remains of thymus scattered throughout the thymic fat with large corpuscles of Hassall, many of which are calcified.

Spleen.—Marked acute passive congestion. Small hemorrhages scattered throughout the pulp. Acute lymphoid exhaustion. Follicles very small with central exhaustion and degeneration. No degeneration of the central portion of the follicles seen as in burns of the skin. No thrombi, no emboli or infarcts.

Adrenals.—Slight cloudy swelling of the cortex. No increase in fat content. Congestion. Edema. Chromaffinic substance small in amount.

Kidneys.—Intense congestion. Cloudy swelling, particularly of the convoluted tubules. Numerous small precipitates of phosphates in the straight tubules of the cortex (concentrated urine). Marked edema of the connective tissue around the larger vessels and of the medullary portion. Very few casts. Frozen sections show no fat.

Bladder.—Congestion and edema. Otherwise negative.

Prostate.—Congestion. Gland spaces filled with secretion and desquamated epithelium. No pathologic changes. The prostatic plexus contains an organizing thrombus.

Seminal Vesicles.—Negative. The one apparently hyaline, shows only collapse of the wall; empty but no fibrosis.

Posterior Urethra.—Negative.

Testes.—Very little normal spermatogenesis. Many atypical division figures and desquamation of spermatids. Stroma is increased throughout, basement membrane thickened. Appearances suggest an old mumps orchitis. Intense congestion of the vessels.

Epididymes.—Negative.

Penis.—Foreskin edematous. Vessels congested, with areas of complete necrosis of the epithelium and of the subepithelial tissues. Where the epidermis is intact the horny layer is thickened and the epithelium beneath shows evidences of regeneration. The glans shows likewise areas of necrotic epithelium with areas of regeneration and other patches in which the horny layer is greatly thickened and adherent. The meatus shows a slight inflammation. The body of the penis shows areas of regenerating epithelium covered with a dense desquamated horny layer. Large areas of the surface are denuded, the epithelium necrotic, the necrosis extending into the subepithelial tissues. Marked congestion and edema throughout the organ and a mild diffuse inflammation.

Liver.—Acute passive congestion. Slight cloudy swelling. Fat stains show no fatty degeneration but a few scattered cells containing large droplets of fat.

Pancreas.—Congestion. Early postmortem softening. No other pathologic changes. Islands numerous, many of them very large.

Stomach.—Postmortem digestion of upper part of mucosa. Congestion. Hemorrhages.

Duodenum.—Postmortem necrosis of mucosa. Marked mucoid change in glands of Brunner.

Small Intestine.—Postmortem desquamation of epithelium. Congestion. Edema. Slight catarrh.

Colon.—Similar changes.

Appendix.—Evidences of old inflammation. No active process.

Mesenteric Glands.—Lymphoid hyperplasia, with exhaustion of the germ centers. Marked sinus catarrh. Many hemophages.

Retroperitoneal Hemolymph Nodes.—Marked congestion of sinuses. Great numbers of hemophages.

Skin.—The skin taken from various portions of the body shows complete necrosis of the epidermis and greater part of the corium reaching as far as the sweat glands over the greater part of the surface, but in many instances reaching the subcutaneous tissues. Many colonies of bacteria are found upon the necrotic corium but there is very little leucocytic infiltration in the necrotic corium or at the border between the living and dead tissues. Only in scattered areas where there is evidently a localized secondary infection are there any notable collections of polynuclears. The vessels in the lower portion of the corium show intense congestion, stasis. In the lymphatics there is a heavy albuminous precipitate with coarse fibrin threads. The lower border of the corium and upper portion

of the subcutaneous fat shows usually a well-marked edema. No old thrombi are found and very few hemorrhages, only here and there have a few red blood cells escaped from the vessels. More recent clots with heavy threads of fibrin are found in many of the distended vessels. In these clots many hemolyzed red blood cells are seen. Some hyaline clots are found in the areas of marked necrosis and secondary infection, but these may be secondary to the latter process. Fibroblastic proliferation has begun at the lower border of the necrotic corium and is particularly marked around many of the blood vessels and sweat glands. Regeneration of epithelium from the hair follicles and sweat glands has begun in many areas and in some instances extends to the surface. Separation of the eschar has begun in some areas. Every degree of change is shown from areas where the necrotic epithelium is still adherent, to those areas where the slough is beginning to separate, and to areas of beginning regeneration. A striking feature of the process is that the sebaceous glands are everywhere completely necrosed, but islands of regenerating squamous epithelium mark the site of these glands. The sweat glands also show marked degeneration, the majority of the acini being necrotic or hydropic. Regeneration of epithelium occurs almost entirely from the hair follicles and ducts of the sweat glands. Around the nipple, in the axillary region and over the scrotum the necrosis is deeper and more marked and the large sweat glands of the axilla show marked degeneration. In the scrotum the necrosis extends deep into the dartos involving the superficial bundles of involuntary muscle. In the scrotum, also, regeneration of epithelium proceeds from the hair follicles.

FINAL PATHOLOGIC DIAGNOSIS.—Mustard gas burns of skin and upper respiratory tract. Necrosis, secondary infection and gangrene of skin. Acute necrotic pharyngitis. Acute catarrhal laryngitis, tracheitis and bronchitis. Congestion and edema of lungs. Multiple hemorrhagic infarctions of lungs. Acute passive congestion of all organs. Multiple petechial hemorrhages. Marked fatty degeneration of intima of aorta. Parenchymatous degeneration of kidneys and liver. Splanchnic congestion. Shock. Toxemia. Secondary anemia. Hypoplasia of heart and aorta. Thymicolymphatic constitution. Hyperplasia of hemolymph nodes with excessive hemolysis. Organizing thrombus in prostatic plexus. Old orchitis (mumps?).

SUMMARY OF CASE

The pathological findings in this autopsy case give no evidence of a systemic action of dichlorethylsulphide. All of the changes seen can be explained as due to the direct local action of the mustard gas vapor, or as secondary to the shock and secondary infection of the lesions.

III. GENERAL PATHOLOGY RESULTING FROM SUBCUTANEOUS AND INTRAVENOUS INJECTIONS OF DICHLORETHYLSULPHIDE

Series of animals, rabbits and dogs, were given varying amounts of dichlorethylsulphide by subcutaneous and intravenous injection. Two samples of very pure dichlorethylsulphide were used, one furnished by Major Moses Gomberg, and the other by the Chemical Warfare Service. For the subcutaneous injections in rabbits, a site on the right side of the back was constantly employed. The hair was clipped or shaved over an area six centimeters in diameter and the liquid dichlorethylsulphide was injected into the subcutaneous fascia above the spinal muscles. In dogs, also, the injection was made beneath the skin of the back. For the intravenous injections in rabbits, the superficial femoral and jugular veins were used. The pure substance was used, instead of oily solutions, because of the great danger of fatty embolism with the latter. In most cases, the animals were allowed to die, but some were killed in order to avoid postmortem change in the tissues. In all cases, autopsies were done, the tissues were fixed in formol, and sections of all organs were stained in hematoxylin and eosin, and other routine stains.

(A) SUBCUTANEOUS INJECTION OF DICHLORETHYLSULPHIDE

The following condensed protocols are selected as representative of the reactions following injection of varying amounts of dichlorethylsulphide. Rectal temperatures, daily weights and character of feces are given, and these, taken together, serve to indicate the severity of the reaction.

RABBIT 55.—Subcutaneous injection of .015 c.c. of dichlorethylsulphide. Very slight general reaction, with apparently complete recovery, except for the local lesion, twenty-six days after injection.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 16	102.3°	1870	.015 c.c. dichlorethylsulphide subcutaneously.
" 17	102.5	1750	No diarrhea.
" 18	102.7	1740	" "
" 19	102.6	1870	" "
" 20	103.1	1880	" "
" 21	102.6	1930	" "
" 22	102.6	1950	Slight diarrhea.
" 23	103.2	2010	No diarrhea.
" 24	103.5	1970	" "
" 25	102.6	2010	" "
" 26	102.6	2060	" "
" 27	103.0	2100	" "
" 28	103.3	2200	" "
" 29	104.1	2090	" "
" 30	103.4	2200	" "
" 31	103.1	2130	" "
Jan. 1	102.8	2120	" "
" 2	103.3	2070	" "
" 3	103.0	2140	" "
" 4	102.6	2150	" "
" 5	103.3	2130	" "
" 6	102.8	2090	" "
" 7	103.0	2090	" "
" 8	103.4	2090	" "
" 9	103.5	2150	" "
" 10	102.2	2300	" "
" 11	102.8	2190	No diarrhea. Lesion is now nearly healed. There is a hairless area about 1 cm. in diameter, which is covered with a shiny smooth cicatrix except for a small area in its central portion.

RABBIT 48.—Subcutaneous injection of .03 c.c. of dichlorethylsulphide. Slight general reaction. Living, thirty-seven days after injection, with apparent complete recovery, except for the local lesion.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 5	101.6°	2100	.03 c.c. dichlorethylsulphide subcutaneously. No signs of local irritation.
" 6	102.6	2020	No diarrhea. Animal very thirsty.
" 7	102.0	2050	" "
" 8	103.0	2060	" "
" 9	101.0	1990	" "
" 10	101.8	1940	Slight diarrhea.
" 11	103.6	1950	No evidence of diarrhea.
" 12	102.4	1990	Perianal hair somewhat soiled.
" 13	103.6	1900	No diarrhea.
" 14	104.4	1870	" "

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES (Cont'd from p. 274.)
Dec. 15	103.9	2000	No diarrhea.
" 16	103.2	2030	" "
" 17	102.7	1930	" "
" 18	102.6	1830	" "
" 19	101.6	1810	" "
" 20	102.6	2040	" "
" 21	103.6	2000	" "
" 22	102.2	2080	" "
" 23	102.1	2110	" "
" 24	102.7	2090	" "
" 25	103.3	2000	" "
" 26	101.6	2060	" "
" 27	102.0	2070	" "
" 28	102.3	2150	" "
" 29	103.5	2110	" "
" 30	103.7	2140	" "
" 31	103.6	2170	" "
Jan. 1	103.1	2020	" "
" 2	102.9	2030	" "
" 3	102.8	2250	" "
" 4	103.5	2170	" "
" 5	103.2	2060	" "
" 6	103.4	2020	" "
" 7	103.2	1990	" "
" 8	102.1	2020	" "
" 9	102.6	2060	" "
" 10	102.8	2240	" "
" 11	102.6	2100	No diarrhea. The local lesion is not yet completely healed. There is an indurated area about 1 by 1.5 cm. over which there is an incomplete regeneration of epithelium. This area is firmly adherent to the underlying tissue.

RABBIT 47.—Subcutaneous injection of .03 c.c. of dichlorethylsulphide. Moderately severe reaction. Death on the twelfth day.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 5		102.5°	1520	.03 c.c. dichlorethylsulphide subcutaneously. No evidence of local reaction.
" 6		102.8	1430	No diarrhea.
" 7		102.1	1490	No diarrhea. Edematous area at site of injection measures 2 by 6 cm.
" 8		101.8	1460	No diarrhea.
" 9,	9:30 A.M.	97.6	1380	" "
" 9,	10:30 P.M.	97.0		Hair soiled about anus and soft fecal material on thermometer.
" 10,	9:30 A.M.	98.6	1250	Diarrhea.
" 10,	5:00 P.M.	96.0		"
" 11,	9:00 A.M.	99.0	1120	"
" 11,	5:00 P.M.	96.7		"
" 12,	9:30 A.M.	99.8	1155	"
" 12,	4:30 P.M.	100.2		Hair soiled, but feces formed.
" 13		101.6	1100	No diarrhea.
" 14		101.5	1060	" "
" 15		100.8	1060	" "
" 16		101.7	1070	" "
" 17		97.2	995	Appears much sicker. Perianal hair soiled, but no diarrhea noted.
" 17,	1:00 P.M.			Died.

AUTOPSY

Autopsy at 1:45 P.M. Body warm. No rigor. *Pleural cavities* and *pleuræ* negative. *Heart* contracted. The right auricle still pulsates when stimulated. The *lungs* show a moderate congestion with hypostatic areas posteriorly in the lower lobes. The *liver* is congested, otherwise negative. The *gall bladder* is not distended. The spleen shows a moderate congestion, likewise the *kidneys*, in which there are also some edema and slight cloudy swelling. The *stomach* is nearly empty and the mucosa shows no changes. The upper small *intestines* are slightly edematous. Formed stools are found in the *colon*. No evidence of diarrhea. At the root of the mesentery there is a lobulated mass of edematous hyperplastic lymph nodes.

MICROSCOPIC FINDINGS.—*Lungs*. Slight congestion. No edema. *Heart*. Negative. *Spleen*. Congestion. In the sinuses are great numbers of pigmented hemophages, the pigment varying in color from brown to almost black. Hemosiderosis. *Kidneys*. Moderate congestion. Very slight cloudy swelling. Practically negative. *Adrenals*. Negative. *Stomach*. Negative. *Small Intestine*. Congestion and edema of mucous membrane with necrosis of the superficial epithelium of the tops of the folds and villi. Glands of Lieberkühn show excessive mucus formation and individual glands show necrosis. Minute erosions occur along the mucosa. The *liver* shows marked passive congestion, a nutmeg liver with acute central necrosis in many lobules. The bile ducts show an unusual mucous degeneration of the epithelium with edema of the surrounding connective tissue. There is a complete necrosis of the epithelium of the *gall bladder* and of its basement membrane. The neighboring liver tissue also shows a zone of necrosis as from the diffusion of some necrosing substance from the gall bladder. At the *site of injection* there is a large area of necrosis extending through the striped muscle into the fascia. About this, there is a zone of fibroblastic proliferation and leucocyte infiltration. The striped muscle in the neighborhood shows a marked Zenker's necrosis.

RABBIT 50.—Subcutaneous injection of .06 c.c. of dichlorethylsulphide. Moderately severe reaction. Apparent recovery, except for local lesion. Animal killed on the 32nd day after injection.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 6		101.7°	2020	.06 c.c. dichlorethylsulphide subcutaneously.
" 7		101.8	2000	No diarrhrea. Very thirsty.
" 8		101.6	2130	No diarrhea.
" 9		100.0	2060	" "
" 10,	9:30 A.M.	100.9	1990	" "
" 10,	5:00 P.M.	98.6		Perianal hair somewhat soiled.
" 11,	9:00 A.M.	100.0	1920	Diarrhea.
" 11,	5:00 P.M.	98.6		Marked foul diarrhea.
" 12,	9:30 A.M.	99.6	1840	Diarrhea.
" 12,	4:30 P.M.	101.7		Perianal hair still soiled.
" 13		102.6	1790	" " " "
" 14		102.6	1840	Stool slightly soft.
" 15		102.4	1820	" " "
" 16		102.7	1840	Perianal region still somewhat soiled.
" 17		101.8	1710	No diarrhea.
" 18		102 0	1650	" "
" 19		102.3	1640	" "
" 20		102.2	1740	No diarrhea. Quite weak.
" 21		103.0	1710	" "
" 22		101.8	1660	No diarrhea. Weak and appears very sick.
" 23		102.9	1680	No diarrhea. Appears stronger.
" 24		103.0	1650	" "
" 25		103.2	1680	" "
" 26		102.6	1740	" "
" 27		104.0	1780	" "
" 28		102.7	1800	" "

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES (*Cont'd from p. 276.*)
Dec.	29	102.9	1810	No diarrhea.
"	30	103.9	1910	" "
"	31	103.6	1950	" "
Jan.	1	103.6	1900	" "
"	2	103.4	1870	" "
"	3	102.9	1910	" "
"	4	103.2	2030	" "
"	5	102.9	1940	" "
"	6	102.7	1930	" "
"	7	102.9	1970	No diarrhea. The local lesion now measures 15 by 30 mm. It is dry, nonpurulent and shows slowly progressing healing.
"	7, 2:30 P.M.			Animal killed. Autopsy at once.

AUTOPSY

Pleuræ, pleural cavities, heart and *lungs* are negative. The *stomach* is distended with food; its mucosa appears negative. The *gall bladder* is small; the bile, pale. *Liver.* Congestion. *Spleen.* Congestion. *Kidneys.* Slight cloudy swelling and congestion. The upper small *intestines* contain a small quantity of thin fluid material. There are no formed stools in the colon, but no evidence of diarrhea. The intestinal mucosa shows no lesions to the naked eye.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Congestion without edema. Small patches of bronchopneumonia. *Spleen.* Marked congestion with a fairly large number of pigmented phagocytes. *Kidneys* and *adrenals.* Negative. *Stomach.* Negative. Mucosa well preserved. *Liver.* Congestion. Slight cloudy swelling. Bile ducts negative. *Gall bladder.* Epithelium well preserved. No necrosis. *Intestine.* Marked catarrhal enteritis. Epithelium well preserved. No desquamation. Lumen nearly empty. *Pancreas.* Congestion. *Mesenteric lymph nodes.* Extreme edema.

RABBIT 63.—Subcutaneous injection of .06 c.c. of dichlorethylsulphide. Severe reaction. Animal killed on the fifteenth day.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 23	105.0°	2810	.06 c.c. dichlorethylsulphide in deep subcutaneous and intramuscular injection.
" 24	103.6	2770	No diarrhea.
" 25	103.0	2580	" "
" 26	102.0	2610	Slight diarrhea.
" 27	102.1	2580	Diarrhea.
" 28	99.7	2500	"
" 29	98.5	2450	Marked diarrhea.
" 30	100.9	2260	" "
" 31	101.6	2120	" "
Jan. 1	101.8	2130	Diarrhea.
" 2	103.0	2050	Stools formed but moist. Marked edema of right half of abdominal wall.
" 3	102.9	2060	No diarrhea.
" 4	103.4	2100	" "
" 5	103.1	1950	" "
" 6	102.0	1920	" "
" 7	100.5	1840	" "
" 7, 1:30 P.M.			Killed. Autopsy at once.

AUTOPSY

Pleural cavities, pleuræ, heart and *lungs* negative, except for numerous firm, slightly caseous areas at root of right lung, probably an old tuberculosis. *Peritoneal cavity* contains about 50 c.c. of clear fluid. *Liver.* Congestion. *Gall bladder.* Moderately distended with thin bile. *Stomach.* Moderately filled. No visible lesions of the mucosa. *Intestines.* Peristalsis very active. Thin mucoid fluid in upper small intestine. In the cecal pouch there is much thick gruel-like fecal material with denser oval masses adherent to the mucosa. Formed stools in colon. *Kidneys.* Congestion and slight cloudy swelling. *Adrenals.* Congestion. *Mesenteric nodes.* Somewhat hyperplastic.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Pulmonary abscesses. Congestion. *Spleen.* Marked congestion. No pigmented phagocytes. *Kidneys.* Congestion, otherwise negative. *Adrenals.* Excess of fat. Marked lipoidosis of fascicular and reticular zones. *Stomach.* Negative. *Intestines.* Epithelium well preserved for the greater part. No mucoid degeneration except in one portion, where the mucous glands are distended and filled with hyaline cast-like masses. Many of the glands are shallow mucous cysts. *Liver.* Cells small, simple atrophy. *Gall bladder.* Epithelium perfectly preserved. No necrosis. Papillæ less marked than normal. Submucosa edematous. *Site of injection.* Large area of necrotic muscle. Deposit of lime salts. Bacterial infection.

RABBIT 65.—Subcutaneous injection of .12 c.c. of dichlorethylsulphide. Very severe reaction. Death on the fifth day.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 23	104.3°	2750	.12 c.c. dichlorethylsulphide subcutaneously.
" 24	104.9	2580	No diarrhea.
" 25	102.0	2470	Beginning diarrhea.
" 26	102.8	2410	Diarrhea.
" 27	100.8	2310	Slight diarrhea.
" 28	97.2	2200	Very severe diarrhea.
			Died during the night of Dec. 28 to 29.

AUTOPSY

Body cold. Marked rigor. Entire posterior portion of body is soaked with fluid feces. At the site of injection there is a small brownish area. On incising this area, the subcutaneous fascia is found to be a bright sulphur yellow in color. There is very little local edema. *Pleural cavities* and *pleuræ* are negative. The *heart* shows a slight dilatation. There is a moderate congestion of the *lungs* most marked posteriorly. The *peritoneum* is negative and there is no fluid in the abdominal cavity. The *liver* is firm, deeply fissured, and shows a marked congestion. The *gall bladder* is nearly empty, collapsed, its wall wrinkled. It contains but a few drops of a thin yellowish mucoid fluid. The *stomach* is moderately distended. The stomach mucosa appears negative. The *spleen* and *kidneys* show congestion; otherwise they are negative. *Adrenals.* Negative. The *intestines* contain only fluid fecal material. No lesions of the intestinal tract can be seen. All *splanchnic* veins show a marked congestion.

MICROSCOPIC FINDINGS.—*Heart.* Negative. Large white clot in right ventricle. *Lungs.* Intense congestion and edema. Patches of atelectasis. One of the pulmonary arteries contains a large laminated thrombus or embolus, rich in leucocytes. *Spleen.* Intense congestion. In the sinuses there are great numbers of phagocytes containing hemosiderin. *Kidneys.* Congestion, otherwise negative. *Adrenals.* In one adrenal there is an area of fibrosis. *Liver.* Intense congestion. Cloudy swelling. Cirrhosis. Coccidiosis. *Gall bladder* is completely necrotic. Necrotic diffusion zone in surrounding liver tissue. The larger bile ducts show hyaline swelling of their columnar epithelium. Excessive mucus formation. *Stomach.* Postmortem change, otherwise negative, except at the pyloric end, where there is a marked mucoid degeneration. *Intestine.* Extreme catarrh. All glands show extreme mucous degeneration. Desquamation of the epithelium. *Skin lesion.* Large area of necrosis. Hemorrhage. Edema. No reaction.

RABBIT 64.—Subcutaneous injection of .12 c.c. of dichlorethylsulphide. Se-

vere reaction. Death on sixth day. The close parallelism between this case and the preceding is noteworthy.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 23	103.7°	2500	.12 c.c. dichlorethylsulphide subcutaneously.
" 24	103.5	2260	No diarrhea. Some edema of abdominal wall on the right side.
" 25	103.1	2210	No diarrhea. Edema continues.
" 26	103.4	2110	" " " "
" 27	103.4	2040	Moderate diarrhea.
" 28	103.2	1920	Slight diarrhea.
" 29	97.6	1830	Marked diarrhea.
			Died during the night of Dec. 29. to 30.

AUTOPSY

Body cold. No rigor. Edema of abdominal wall has diminished. There is a small red-brown eschar at the site of injection. *Heart.* Moderate dilatation. Fibrin and leucocyte clot in right auricle. *Lungs* are somewhat mottled, particularly in upper lobes, probably an early lobular pneumonia. Congestion. *Peritoneum.* Moist shining. *Liver.* Congested. *Gall bladder.* Well filled. Bile, thin and greenish yellow in color. Small *intestines* and greater part of colon distended with very abundant yellowish brown fluid fecal material. Formed stools in descending colon. *Kidneys.* Moderate congestion. *Splanchnic vessels* all show marked congestion.

Microscopic Findings.—*Heart.* Negative. Large white clot with very few leucocytes. *Lungs.* Purulent bronchopneumonia. Marked congestion and edema. There is a large thrombus of a pulmonary vessel, the wall of which shows necrosis. Around the vessel there is a zone of necrosis which shades off to partial necrosis, as though due to the diffusion of a necrosing substance from the vessel. There are enormous numbers of staphylococci throughout the lung. *Kidneys.* Congestion. Numerous casts in one. *Gall bladder.* Wall completely necrosed, with area of diffusion necrosis in surrounding liver tissue. *Liver.* Congestion. Cloudy swelling. Small areas of lime salt deposit in necrotic liver cells. Some of the larger bile ducts show a polynuclear infiltration around the columnar epithelium. The epithelium itself shows a slight cloudy swelling. *Adrenals.* Increased lipoid content in cortex. Congestion of medulla. *Stomach.* Negative. *Intestines.* Marked desquamative catarrh. Necrosis of upper portion of mucosa. Extreme mucoid degeneration of the glands. *Site of injection.* Enormous area of necrosis extending clear through the skin and subcutaneous tissues. Hemorrhage. Thrombosis. Areas of polynuclear infiltration. Secondary infection.

Rabbit 67.—Subcutaneous injection of .18 c.c. of dichlorethylsulphide. Very severe reaction. Severe diarrhea within 24 hours and death during the third day.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 27,	3:30 P.M.	102.2°	1660	.18 c.c. dichlorethylsulphide subcutaneously.
" 28,	11:00 A.M.	98.2	1570	Marked diarrhea.
				Died during the night of Dec. 28 to 29.

AUTOPSY

Body cold. Rigor mortis present. Head retracted. Fur about the anus is wet with liquid feces. The abdominal wall shows a marked edema which extends up the right flank. At the site of injection the subcutaneous tissues show but very little edema and no surface lesion is visible. Upon incising this area the fascia is found to be yellow in color. *Pleural cavities* and *pleuræ* are negative. *Heart.* Moderate dilatation. Blood

coagulated. *Lungs.* Marked congestion. *Peritoneum.* Moist shining. No free fluid in peritoneal cavity. *Liver.* Congestion. *Gall bladder.* Moderately filled with thin bile. The *stomach* is partly distended. Its wall is somewhat edematous and in the mucosa several minute erosions are visible. *Spleen* and *kidneys.* Congestion. *Adrenals.* Negative. The *intestines* are distended with gas and fluid feces. Marked diarrhea. Splanchnic congestion.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Congestion. Some edema. Areas of atelectasis. *Spleen.* Congestion without pigmentation. *Kidneys, adrenals* and *pancreas.* Negative. *Liver.* Congestion. Slight cloudy swelling. The larger bile ducts show desquamation of the epithelium and some of them are completely necrosed. *Gall bladder.* The wall is completely necrosed and there is some necrosis from diffusion into the surrounding liver tissue. *Stomach.* Negative. *Intestines.* Catarrhal enteritis. Marked mucoid degeneration throughout.

RABBIT 66.—Subcutaneous injection of .18 c.c. of dichlorethylsulphide. Severe diarrhea. Marked fall in temperature. Death on the eleventh day.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 27	103.7°	2550	.18 c.c. of dichlorethylsulphide subcutaneously.
" 28	102.0	2350	No diarrhea. Marked edema of abdominal wall.
" 29	101.6	2320	" " " " " " "
" 30	101.0	2260	" " " " " " "
" 31	99.6	2200	" " " " " " "
Jan. 1	99.4	2160	" " " " " " "
" 2	98.0	2160	No diarrhea. Edema somewhat less.
" 3	97.0	2080	Diarrhea.
" 4	97.1	1890	Marked diarrhea.
" 5	95.0	1610	Marked diarrhea. Left eye sealed with exudate. (Terminal secondary infection.)
" 6	94.0—	1540	Marked diarrhea. Both eyes sealed with mucopurulent exudate. Died during the night of Jan. 6 to 7.

AUTOPSY

Body still warm. No rigor. Both eyes sealed with exudate. When lids are separated, a large quantity of mucopurulent exudate escapes. No superficial lesion at site of injection and only a slight subcutaneous induration can be felt. There is a firm mass, about 2.5 cm. in diameter, in the abdominal wall at the site of the marked edema noted while the animal was living. On incising this mass it is found to be somewhat edematous still, and the tissues are stained a bright sulphur yellow color. *Heart.* Right-sided dilatation. *Lungs.* Pale pink in color. Slight congestion. *Liver.* Marked congestion. *Gall bladder.* Distended. Bile highly pigmented. *Stomach.* Nearly empty; its contents bile-stained and very mucoid. In the mucosa there are numerous small erosions, particularly in the fundus, along the greater curvature. These are covered with an abundant mucus and have shreds of brownish red material, probably blood clot, streaking the mucus over them. *Spleen.* Negative. *Kidneys.* Congestion and slight cloudy swelling. The *intestines* contain gas and a small quantity of fluid material. There are no formed stools. *Adrenals.* Congestion.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Moderate congestion. Emphysema. No edema. *Kidneys.* One kidney shows many casts in the medullary tubules. Otherwise negative. *Spleen.* Markedly congested, with a fairly large number of pigmented phagocytes. *Liver.* Congestion and cloudy swelling. *Stomach.* Extreme mucoid degeneration of the epithelium of the outer portion of the mucosa, with desquamation. Marked cloudy swelling of the parietal cells. Small postmortem erosions. *Gall bladder.* Mucosa fairly well preserved. No necrosis of wall or neighboring liver tissue. *Intestines.* Marked mucoid degeneration. Extreme catarrhal enteritis.

RABBIT 69.—Subcutaneous injection of .24 c.c. of dichlorethylsulphide. Diarrhea. Death within twelve hours.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 30, 3:45 P.M.	103.9°	1660	.24 c.c. of dichlorethylsulphide subcutaneously. No evidence of local irritation. Died during the night of Dec. 30 to 31.

AUTOPSY

Body cold. Rigor present. Soft formed stools matted in hair about anus. No superficial lesion at site of injection, only a slight subcutaneous edema. Upon incising this area, there is a very strong odor of dichlorethylsulphide. *Heart.* Marked dilatation. *Lungs.* Congestion, with small hemorrhages beneath the pleura of the diaphragmatic surfaces of the lower lobes. *Liver.* Congestion. *Stomach.* Moderately distended. No lesions of mucosa visible. *Spleen, kidneys* and *adrenals.* Congestion, otherwise negative. *Intestines.* Distended with gas and fluid fecal material. No formed stools. Marked splanchnic congestion.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Congestion. Edema. Small capillary hemorrhages. *Adrenals.* Negative. *Spleen.* Congestion. No pigmented phagocytes. *Pancreas.* Negative. *Kidneys.* Rather marked cloudy swelling, even to simple necrosis. *Gall bladder.* Complete necrosis of wall, necrosis extending into liver tissue for some distance. Slight cloudy swelling of the liver cells. *Stomach.* Negative. *Intestines.* Congestion, otherwise negative. *Site of injection.* Large area of necrosis. Edema. No reaction.

RABBIT 70.—Subcutaneous injection of .30 c.c. of dichlorethylsulphide. Diarrhea. Death within twelve hours.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 30. 4:15 P.M.	104.0°	1810	.30 c.c. of dichlorethylsulphide subcutaneously. No evidence of local irritation. Died during the night of Dec. 30 to 31.

AUTOPSY

Body cold. Rigor present. Much soft fecal material about the anus. Strong odor of dichlorethylsulphide when area of injection is excised. *Heart.* Marked dilatation. *Lungs.* Congestion, otherwise negative. *Liver, spleen, kidneys* and *adrenals.* Congestion. *Gall bladder.* Well filled. *Intestines.* The upper portion of the small intestine is filled with yellowish fluid material. No formed stools in lower colon. Marked splanchnic congestion.

MICROSCOPIC FINDINGS.—*Heart.* Hypertrophy and dilatation. *Lungs.* Intense congestion and edema. *Spleen.* Congestion. Very few pigmented phagocytes. *Pancreas.* Negative. *Adrenals.* Congestion. *Kidneys.* Congestion and some cloudy swelling. *Liver.* Congestion and fatty degeneration. *Gall bladder.* Necrosed. Diffusion zone of necrosis in the surrounding liver tissue. *Intestines.* Epithelium well preserved. Early stage of mucous degeneration; practically every cell filled with mucus and the majority of them intact. *Site of injection.* Large eschar involving all tissues.

RABBIT 72.—Subcutaneous injection of .60 c.c. of dichlorethylsulphide. Death on the second day.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 31, 3:15 P.M.	102.7°	3050	.60 c.c. of dichlorethylsulphide subcutaneously. No evidence of local irritation. Animal eating in five minutes.
4:00 P.M.			Sits quietly. Respiration rate appears somewhat accelerated.
6:00 P.M.	102.5		Quiet. No diarrhea.
7:30 P.M.	102.0		Quiet. Heart regular. Respiration quickened. Seems to be about to roll over on side, but quickly recovers itself.
8:30 P.M.	101.7		No diarrhea.
9:00 P.M.	101.8		" "
9:15 P.M.			No diarrhea. Hopping about and eating.
Jan. 1, 10:00 A.M.	101.1	3010	No diarrhea.
11:00 A.M.	102.3		Soft pasty feces.
2:30 P.M.	102.5		Diarrhea.
			Died during the night of Jan. 1 to 2.

AUTOPSY

Body still somewhat warm. Perianal hair soiled. Very strong odor of dichlorethylsulphide at site of injection. *Heart.* Right-sided dilatation. *Lungs.* Congestion. *Liver, spleen, kidneys* and *adrenals.* Congestion. Otherwise negative. *Stomach.* Moderately distended. In the mucosa there are several small erosions with brownish red bases. *Intestines.* Much fluid material. No formed stools in lower colon. Diarrhea. Edema of *thoracic* and *abdominal walls.*

MICROSCOPIC FINDINGS.—*Brain.* Congestion. *Heart.* Negative. *Lungs.* Congestion without edema. *Spleen.* Intense congestion without pigmented phagocytes. *Kidneys.* Congestion. Otherwise negative. *Stomach.* Negative. Some postmortem change. *Small intestine.* Marked postmortem change, with the picture of a mucous catarrh involving the greater part of the tract. *Liver.* Cirrhosis. Coccidiosis. Large bile ducts dilated; their epithelium well preserved. The small bile ducts are unchanged. Slight fatty degeneration. *Gall bladder.* Nearly complete necrosis of wall. Narrow necrotic zone of diffusion into surrounding liver tissue.

RABBIT 74.—Subcutaneous injection of .60 c.c. of dichlorethylsulphide, .15 c.c. being injected in each of four widely separated areas on the back. Rabbit killed when dying, four hours after injection. No apparent acceleration of reaction with increased opportunity for absorption.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 1, 11:45 A.M.	103.5°	1970	.15 c.c. of dichlorethylsulphide injected in each of four areas. No evidence of local irritation.
2:15 P.M.			Lying on side. Moves legs and head readily. Heart strong and regular. The increased irritability, shown by reaction to sound and jarring of table, suggests that due to strychnine.
4:30 P.M.			Respirations few and gasping. Heart beating vigorously. Diarrhea.
4:45 P.M.			Killed by chloroform. Autopsy at once.

AUTOPSY

Head somewhat retracted. Perianal region covered with soft fecal material. *Heart.* Moderately dilated. *Lungs.* Negative. *Liver.* Congestion. *Gall bladder.* Nearly empty. Negative. The *stomach* is moderately distended. The mucosa of the fundus, particularly

along the greater curvature, shows a large number of small, shallow erosions with dark red-brown bases. *Intestines.* Contain much fluid material. No formed stools in colon.

MICROSCOPIC FINDINGS.—*Liver.* Marked congestion. Slight cloudy swelling. The small bile ducts are apparently normal. *Gall bladder.* Epithelium perfectly preserved. No changes observable. *Stomach.* Well preserved. Portions examined show no changes. *Intestines.* Catarrhal enteritis.

DOG 3.—White bull terrier, weight 8 kilos. Subcutaneous injection of .24 c.c. of dichlorethylsulphide. Severe diarrhea. Death in four days.

Aug. 27.—.24 c.c. of dichlorethylsulphide injected subcutaneously in back.

Aug. 28.—Appears sick. Is much less active and coat is roughened.

Aug. 29.—Appears very sick. No diarrhea.

Aug. 30.—Very severe diarrhea. Stools fluid and brownish black in color, resembling altered blood. The animal remains quiet.

Aug. 31.—12:00 noon. Lying on side. Respiration slow and shallow. Diarrhea persists.

6:00 P. M. Dog died during the afternoon. Autopsy at 7:00 P. M.

AUTOPSY

The body is in complete rigor. The posterior portion is soiled with fluid fecal material. At the site of injection there is an indurated lamellar area, about 10 cm. in diameter, which involves both skin and subcutaneous fascia. *Pleural cavities* and *pleuræ* negative. *Heart.* Marked right-sided dilatation, the left ventricle being in rigor. Small amount of very dark fluid blood in the chambers. *Lungs.* Free throughout. Air-containing. Middle lobe of right lung congested. No pneumonia. No free gas or fluid in *peritoneal cavity. Omentum* free. The subperitoneal vessels over the *intestines* are congested and there are a few minute subperitoneal hemorrhages. The intestines are empty and firmly contracted. The *duodenum* contains a bile-stained fluid and the mucosa is bile stained. Throughout the small intestine the mucosa shows a marked congestion and there are small hemorrhages in the summits of some of the folds. The Peyer's patches are hyperplastic. In the colon the mucosa is much congested and there are a few very minute hemorrhages. The *appendix* is negative. The *stomach* wall is contracted, the rugæ prominent. The mucosa is much congested and there are a few pinpoint hemorrhages. The *kidneys* show slight cloudy swelling. The *adrenals* are well preserved and negative. The *bladder* is contracted; its mucosa, negative.

MICROSCOPIC FINDINGS.—The *heart* shows dilatation and its vessels are congested. *Lungs.* Marked edema. Intense congestion. Small hemorrhages. Several areas of hemorrhagic infarction, with embolic blocking of the vessels. *Spleen.* Congestion. Atrophy. *Kidneys.* Marked congestion. Slight cloudy swelling. *Pancreas.* Marked cloudy swelling. *Liver.* Cloudy swelling. Marked congestion. Marked mucoid degeneration and cloudy swelling of the epithelium of the smaller bile ducts. All of the bile ducts contain a violet-staining, hyaline substance and the epithelium is higher than normal, the cells appearing larger and swollen. The nuclei appear increased in number. The cytoplasm stains violet, but many of the cells are vacuolated. In a few of the larger bile ducts there are small areas of necrosis. The *stomach* mucosa is intact. There is marked congestion and some increase in mucus in the upper portion of the mucosa. The mucosa of the small *intestine* is congested, edematous, and infiltrated with leucocytes. The epithelium of the glands shows syncytial formations of regenerating epithelium. The columnar form of the cells is lost and there is no mucus formation except in the lower small intestine, where there are many mucous cysts, especially in the deeper portions of the mucosa. The fundi of the glands of Lieberkühn are dilated, filled with stringy mucin or a colloid material. The epithelium is cuboidal, or flattened, or syncytial, and stains a deep violet with hematoxylin and eosin. In some of the dilated glands of Lieberkühn the epithelium is entirely gone and the lumen is filled with a hyaline cast. The epithelium of the upper part of the glands and of the surface is entirely gone. The picture is that of a severe degenerative and desquamative catarrhal enteritis with beginning regeneration. The lymph follicles are hyperplastic and the germ centers show lymphoid exhaustion. *Mesenteric nodes.* Marked congestion. Great numbers of hemophages filled with blood cells. *Adrenals.* Marked congestion of medulla. *Site of injection.* A large eschar with marked edema. In the vessels there are large thrombi. The borders of the lesion show an abundant polynuclear infiltration and large areas of hemorrhagic extravasation.

(B) SUBCUTANEOUS INJECTION OF HYDROCHLORIC ACID

Since it has been assumed by some that the local and general effects of dichlorethylsulphide are due to the action of the hydrochloric acid produced by its hydrolytic cleavage, a series of animals was given varying amounts of hydrochloric acid by subcutaneous injection. The following protocol is selected as illustrative of this group.

RABBIT 76.—Subcutaneous injection of .60 c.c. of hydrochloric acid. Both local and general reactions entirely unlike those produced by dichlorethylsulphide.

TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 3, 9:45 A.M.	103.2°	1600	.60 c.c. of hydrochloric acid subcutaneously. Very marked evidence of local irritation. Marked contraction of superficial and deep muscles. The skin "knots up." In about five minutes, evidences of severe pain cease and the animal is eating.
4	103.6	1710	No diarrhea. Very extensive lesion at site of injection. There has been complete destruction of the skin and subcutaneous fascia over an area 4 by 5 cm., so that the muscles of the back are fully exposed.
5	103.4	1600	No diarrhea. The muscle is now exposed over an area 5 by 7 cm. There is a constant oozing of blood from the borders of the deeply excavated lesion.
6	103.8	1490	No diarrhea. Still some bleeding from wound.
6, 8:30 P.M.			Killed by chloroform. Autopsy at once.

AUTOPSY

Large excavated lesion, measuring 5 by 7 cm., at the site of injection. The borders are smooth. The base consists of charred, dry fragmented muscle in coarse bundles and masses. There is no purulent exudate. The whole lesion is nearly black in color, as though charred, and is very foul smelling, with the odor of dry gangrene. *Heart.* Still beating. Negative. *Lungs.* Bright pink in color. Moderate congestion. *Liver.* Congested. Extensive coccidiosis. *Spleen.* Negative. *Stomach.* Contains a small amount of food and water, and much swallowed mucus. There are no visible lesions of the mucosa. The *intestines* are nearly empty except the cecum which is moderately filled. The scant amount of fecal matter in the small intestine is very thin, mucoid, and bile stained. In the lower colon the fecal material is soft and but slightly formed. There is, however, no evidence of diarrhea about the anus.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Congestion. No edema and no hemorrhages. *Liver.* Coccidiosis. No diffusion necrosis into liver tissue around the gall bladder. *Gall bladder.* Epithelium well preserved. No necrosis. No desquamation. Many mucin threads in lumen. *Stomach, intestines, kidneys* and *adrenals.* All negative. *Tissue from site of injection.* Very extensive eschar formation.

(C) SUBCUTANEOUS INJECTION OF DIHYDROXYETHYLSULPHIDE

A series of animals was given varying doses of dihydroxyethylsulphide (hydrolyzed mustard gas) by subcutaneous injection, in order to ascertain whether the severe general effects could be due to the absorption of this substance from the site of injection. The following condensed protocols are selected from this series.

RABBIT 80.—Subcutaneous injection of .30 c.c. of dihydroxyethylsulphide. No local lesion, no diarrhea and no loss of weight.

DATE	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 8	104.6°	2250	.30 c.c. of dihydroxyethylsulphide subcutaneously. No evidence of local irritation, and animal eats at once when released.
" 9	102.8	2210	No diarrhea. No local lesion.
" 10	102.6	2270	" " " " "
" 11	102.8	2240	" " " " "
" 12	101.9	2250	" " " " "
" 13	102.6	2300	" " " " "
" 14	102.0	2300	" " " " "
" 15	101.6	2280	" " " " "
" 17	104.0	2170	" " " " "
" 18	103.6	2180	" " " " "

RABBIT 81.—Subcutaneous injection of .60 c.c. of dihydroxyethylsulphide. No local lesion. No diarrhea.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 8,	9:25 P.M.	104.6°	2110	.60 c.c. of dihydroxyethylsulphide subcutaneously. No evidence of local irritation, and animal eats at once when released.
" 9,	8:30 A.M.	103.2	2100	No diarrhea. Very slight edema at site of injection.
	2:30 P.M.			No diarrhea.
	2:45 P.M.			Killed with chloroform. Autopsy at once.

AUTOPSY

There is a slight congestion of all organs. *Stomach* is well filled, its mucosa grossly negative. *Intestines.* Apparently negative. Formed feces in lower colon. No evidence of diarrhea. The *bladder* contains a very turbid yellowish white urine. No other changes.

MICROSCOPIC FINDINGS.—*Lung.* Slight congestion. No edema. *Kidneys.* Negative. Slight congestion. *Adrenals.* Negative. *Spleen.* Negative. *Liver.* Marked fatty change. *Gall bladder.* Epithelium perfectly preserved. No changes. *Small Intestine.* Slight, but well defined catarrh. Congestion of mucosa. Excessive mucus formation. *Stomach.* Negative.

(D) INTRAVENOUS INJECTION OF DICHLORETHYLSULPHIDE

The following condensed protocols are selected from the various series of intravenous injections. In every case in which dichlorethylsulphide was given, it was injected without dilution. Although bland oils will serve as suitable diluents so far as mutual solubility is concerned, the certainty of producing some degree of fatty embolism, with resulting confusion in the pathologic picture, renders this method inadvisable. In addition, the much greater solubility of dichlorethylsulphide in the oil than in the body fluids may be expected to retard its action and delay the production of its characteristic symptomatology.

RABBIT 53.—Intravenous injection of .06 c.c. of dichlorethylsulphide. General convulsions. Marked reduction of temperature. Prostration. Death in less than three hours.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Dec. 9,	2:50 P.M.	101.5°	1570	.06 c.c. of dichlorethylsulphide given intravenously in superficial femoral vein. Light chloroform anesthesia. Animal made quick recovery from anesthesia, soon moving about.
	3:50 P.M.	94.0		Animal very much weaker. Respiration very rapid. Easily startled by sudden movements or unexpected noises. Slight convulsive movements. No general convulsion.
	3:54 P.M.			First general convulsion, consisting of irregular rapid movements. There is some opisthotonos but the head is drawn chiefly to one side.
	4:15 P.M.			Lies on side. Occasional convulsions.
	4:45 P.M.			Continues to lie on side. Can not turn over. Jerking movements of forepaws, head and neck. Salivation and lacrimation. Pupils dilated. Respiration slow and irregular.
	5:30 P.M.			Death. Much stringy saliva during last fifteen minutes.
	8:00 P.M.			Autopsy.

AUTOPSY

Body nearly cold. Rigor mortis marked. Abdomen moderately distended. No diarrhea. *Pleural cavities* and *pleuræ* negative. *Heart.* Moderately dilated, particularly on the right side. Dark fluid blood, clotting tardily. *Lungs.* Air-containing throughout. Congestion moderate, except posteriorly. *Spleen.* Negative. *Kidneys.* Slight congestion. *Adrenals.* Negative. *Liver.* Marked congestion. Lobules large. Central zones dark red, outer two-thirds of lobule, grayish red. *Gall bladder.* Well filled with a pale mucoid bile. *Stomach.* Distended with food. Mucosa shows scattered areas of postmortem change along greater curvature. Upper small *intestine* contains a thin yellowish mucoid fluid. Lower small intestine is well filled and there are formed stools in the lower colon.

MICROSCOPIC FINDINGS.—*Central Nervous System.* Congestion. *Heart.* Negative. *Lungs.* Congestion. Atelectasis. No edema. No hemorrhage. *Spleen.* Marked congestion but no pigment. *Adrenals* and *pancreas.* Acute congestion. *Stomach.* Slight cloudy swelling of parietal cells. Congestion. *Intestines.* In portion examined the mucosa is well preserved. Congestion of villi. No necrosis. *Liver.* Moderate congestion. Slight fatty degeneration.

RABBIT 51.—Accidental intravenous injection of dichlorethylsulphide in the course of a deep subcutaneous injection. Total injection .12 c.c., of which probably less than .06 c.c. entered a small subcutaneous vein. Convulsions. Diarrhea. Death in four hours.

AUTOPSY

Body still warm but rigor mortis is present. Soft fecal material from anus. Posterior portion of body is much soiled with feces. *Pleural cavities* and *pleuræ.* Negative. *Heart.* Right-sided dilatation. Blood, fluid, clotting slowly. *Lungs.* Free. Slight congestion. Air-containing throughout. *Spleen.* Negative. *Kidneys.* Moderate congestion. *Adrenals.* Negative. *Liver.* Moderate congestion. *Stomach.* Distended with food. The first portion of the small *intestine* contains a very abundant slightly yellow fluid, which is somewhat mucoid. In the descending colon and rectum there are no formed stools.

MICROSCOPIC FINDINGS.—*Heart.* Negative. *Lungs.* Moderate congestion. No edema. Small patches of atelectasis. Bronchioles dilated. No hemorrhages. *Spleen.* Moderate congestion without many pigmented cells, although there are a few. *Kidneys.* Congestion. *Intestine.* Mucosa well preserved. *Stomach.* Negative. *Liver.* Congestion. Slight cloudy swelling.

(E) INTRAVENOUS INJECTION OF HYDROCHLORIC ACID

RABBIT 89.—Intravenous injection of .06 c.c. of hydrochloric acid. Animal living on fourth day. No diarrhea. No evidence of general reaction.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 16,	11:45 A.M.	103.0°	1520	.06 c.c. of strong hydrochloric acid (diluted to 1.20 c.c. with distilled water) in jugular vein.
	1:00 P.M.			Apparently well.
Jan. 17		102.4	1710	No diarrhea.
" 18		103.4	1680	" "
" 20		104.6	1600	No diarrhea. Perfectly well.
" 20				Killed. Autopsy at once.

AUTOPSY

Gross findings all negative, except thrombosis of jugular at site of injection.
MICROSCOPIC FINDINGS.—All negative, except for thrombophlebitis at site of injection.

(F) INTRAVENOUS INJECTION OF DIHYDROXYETHYLSULPHIDE

RABBIT 87.—Intravenous injection of .30 c.c. of dihydroxyethylsulphide. Animal living on the fifth day. No diarrhea. No marked loss of weight.

	TIME	TEMPERATURE DEGREES	WEIGHT IN GM.	NOTES
Jan. 15,	4:00 P.M.	101.6°	2410	.30 c.c. dihydroxyethylsulphide into jugular vein. Light chloroform anesthesia.
	7:00 P.M.			Animal eating. Apparently well.
Jan. 16		103.9	2350	No diarrhea.
" 17		102.6	2320	" "
" 18		102.4	2320	" "
" 20		102.3	2350	No diarrhea. Perfectly well.
" 20				Killed. Autopsy at once.

AUTOPSY.—All gross findings negative.
MICROSCOPIC FINDINGS.—Negative, except for marked fatty liver.

SUMMARY OF EXPERIMENTAL WORK

Subcutaneous Injections.—When pure dichlorethylsulphide is injected subcutaneously in doses of from .015 up to .60 c.c., the injections are apparently painless and the animals exhibit no signs of discomfort. Even with the largest doses the animals resume feeding as soon as released and give no evidence of local irritation. At varying periods of time, from one hour to several days, depending in part upon the size of dose, and in part upon the rate of absorption, toxic symptoms appear, usually in the form of salivation, diarrhea and marked depression of temperature. At first the respirations are quickened; later they become slow. From the largest doses the animal may die within two hours, without diarrhea, but with a short period of nervous excitement followed by coma and gradual failure of respiration. Doses of from .015 to .06 c.c. are

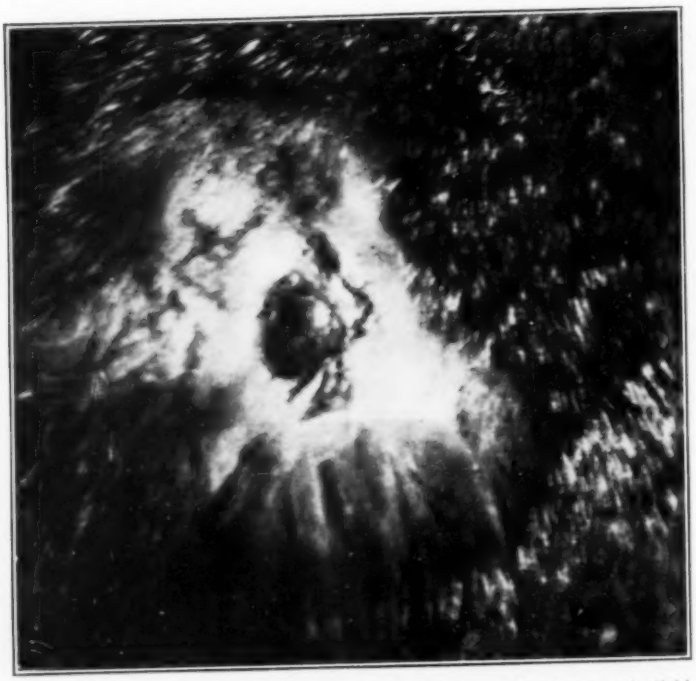

Fig. 1.—Rabbit 58. Eschar resulting from subcutaneous injection of .03 c.c. of dichlorethylsulphide, eighteen days after injection.

Fig. 2.—Rabbit 62. Eschar resulting from subcutaneous injection of .06 c.c. of dichlorethylsulphide, eleven days after injection.

not necessarily fatal to rabbits, although a certain proportion of the animals receiving such doses do die. Death from these doses usually takes place from the fourth to the tenth day. Diarrheal symptoms may appear as early as the second day, but in the great majority of cases diarrhea does not appear until the fourth to seventh day. Coincident with the diarrhea there is a marked fall of temperature, which may be as much as seven to eight degrees below normal. If the animal survives the diarrheal period, the temperature may come back nearly to, or quite to, normal, to fall again just before death, if the animal dies. During the diarrheal stage the animal rapidly loses weight and this loss of weight continues after the cessation of diarrhea, so that when the animal dies, it may

Fig. 3.—Rabbit 76. Sloughing lesion produced by subcutaneous injection of .60 c.c. of hydrochloric acid, twenty-four hours after injection.

have lost as much as one-third of its body weight. The diarrheal stools are fluid, mucoid, brown to black, sometimes tarry, and very foul smelling. Accompanying the diarrhea, there is a marked anorexia and great thirst; the animal is quiet, depressed; and both circulation and respiration are slowed. In the animals that recover, the diarrhea may last for several days, accompanied by a marked lowering of temperature and a general depression. As the stools become normal the temperature rises and the general condition improves until the animal is again apparently perfectly normal.

At the site of the subcutaneous injection there developed a local edema which is usually much less than the edema produced by cutaneous applications. In

a certain number of cases, there is a marked edema of the belly wall, although the injections were routinely made on the back of the animal, apparently due to the hypostasis of body fluid containing mustard gas, from the seat of the injection. The edematous area at the seat of injection gradually changes into an indurated eschar (see Figs. 1 and 2) which undergoes a slow demarcation from the neighboring living tissue. In some animals injected subcutaneously with the dichlorethylsulphide furnished by the Chemical Warfare Service and living two days or longer, a sulphur-yellow coloration of the tissue at site of injection was noted. Such a coloration was not noticed in any animal injected with the Gomberg preparation.

The gross pathology shown by animals killed or dying at varying periods

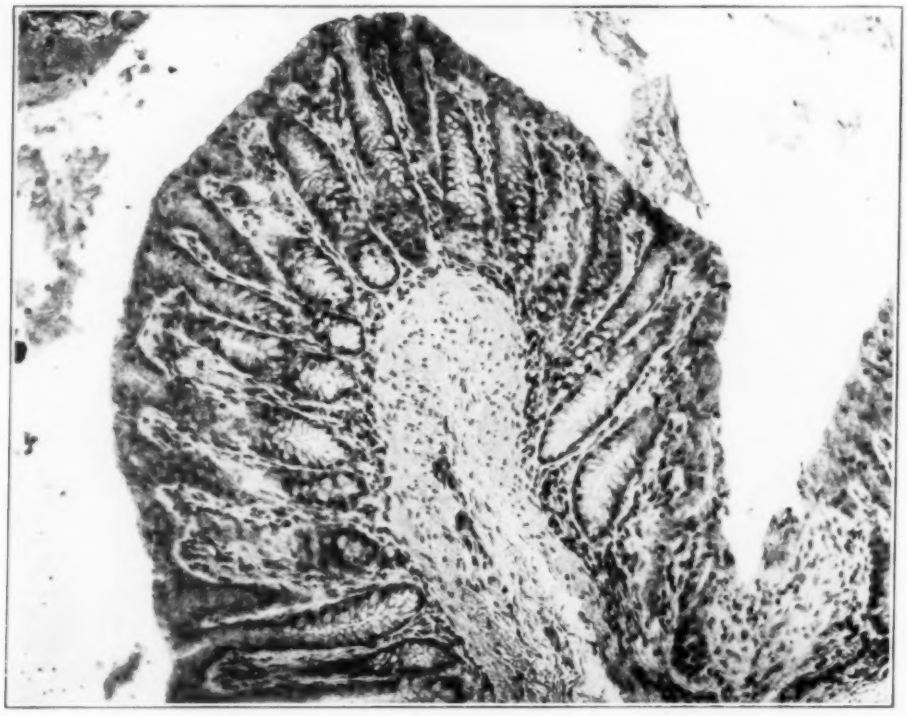

Fig. 4.—Rabbit 59. Received subcutaneous injection of .045 c.c. of dichlorethylsulphide. Died on third day during mild diarrhea. General mucoid degeneration.

after subcutaneous injections consists of a general passive congestion of all organs with occasional minute hemorrhages, emboli, and infarctions. The most specific changes are those found in the gastrointestinal tract in the form of an intense splanchnic congestion and a more or less severe catarrhal enteritis. In practically every instance it was noted that the contents of the gall bladder consisted of a thin, pale, yellowish, mucoid bile.

The microscopic findings confirm the gross appearances. No specific changes are found in any organs except the intestines, spleen, and possibly the bile ducts. These specific changes consist in a mucoid degeneration, necrosis, and desquamation of the epithelium of the intestinal mucosa, marked congestion

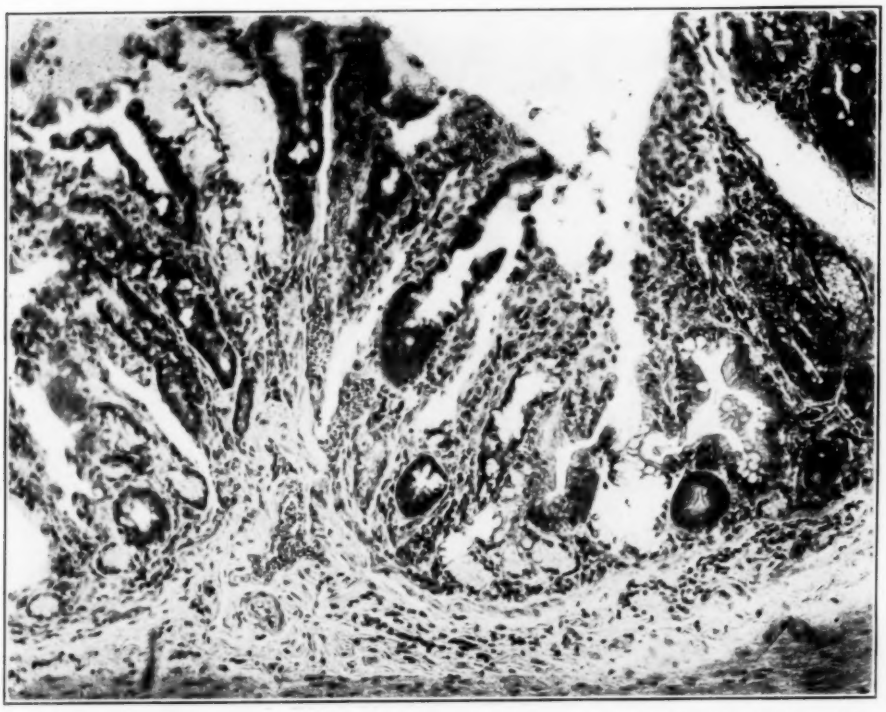

Fig. 5.—Rabbit 66. Received subcutaneous injection of .18 c.c. of dichlorethylsulphide. Began to have diarrhea seven days after injection and died four days later. Section of upper portion of small intestine showing acute catarrhal enteritis.

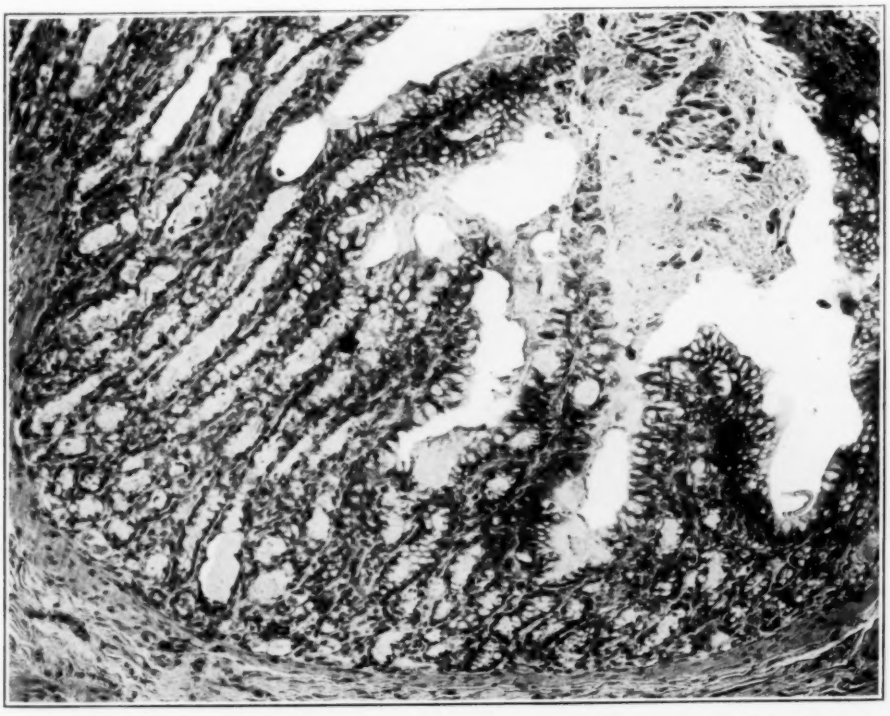

Fig. 6.—Same rabbit as preceding. Extreme mucoid degeneration. Catarrhal enteritis. Mucous diarrhea.

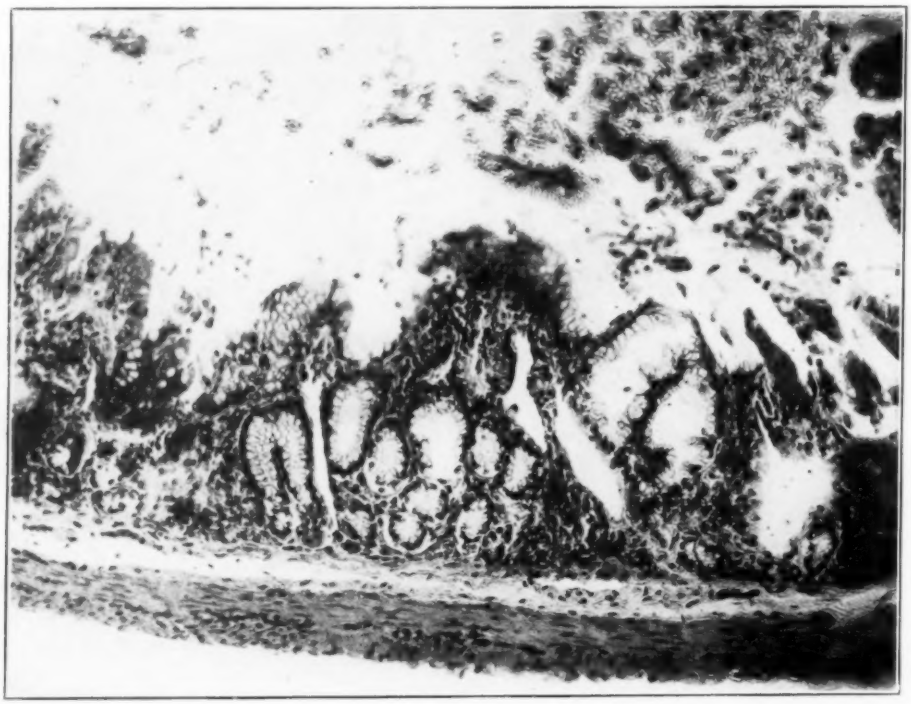

Fig. 7.—Section of cecal wall from same rabbit as preceding. Marked catarrhal inflammation. Mucous diarrhea.

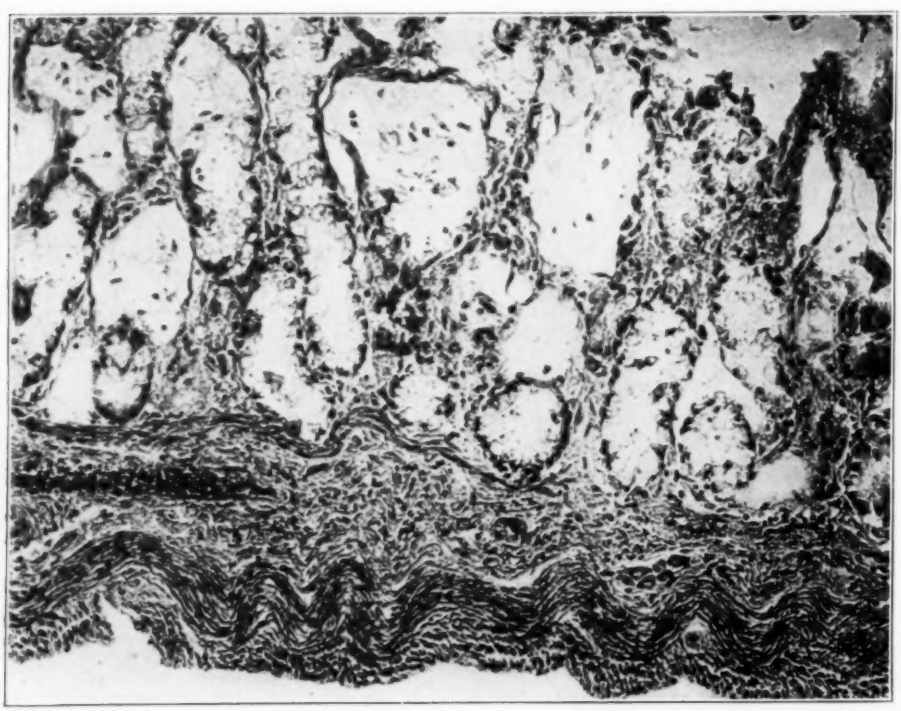

Fig. 8.—Rabbit 65. Received subcutaneous injection of .12 c.c. of dichlorethylsulphide. Diarrhea began on the second day, the animal dying three days later. Extreme mucoid degeneration of the entire intestinal epithelium. Mucous diarrhea.

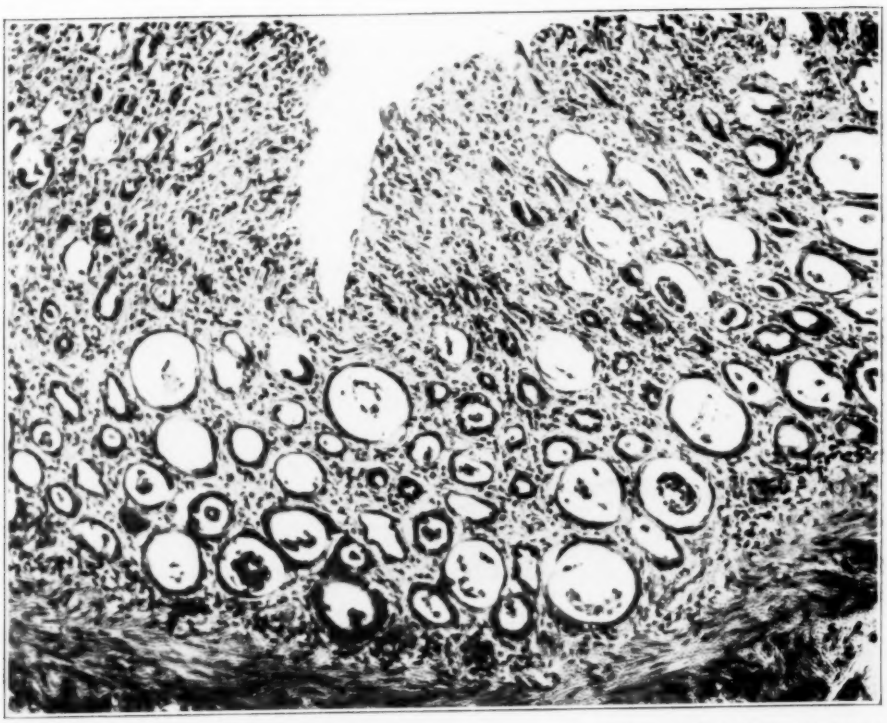

Fig. 9.—Dog 3. Received subcutaneous injection of .24 c.c. of dichlorethylsulphide. Died in four days with a very severe diarrhea. Extreme catarrhal desquamative enteritis. Mucoid degeneration and necrosis of the glandular epithelium.

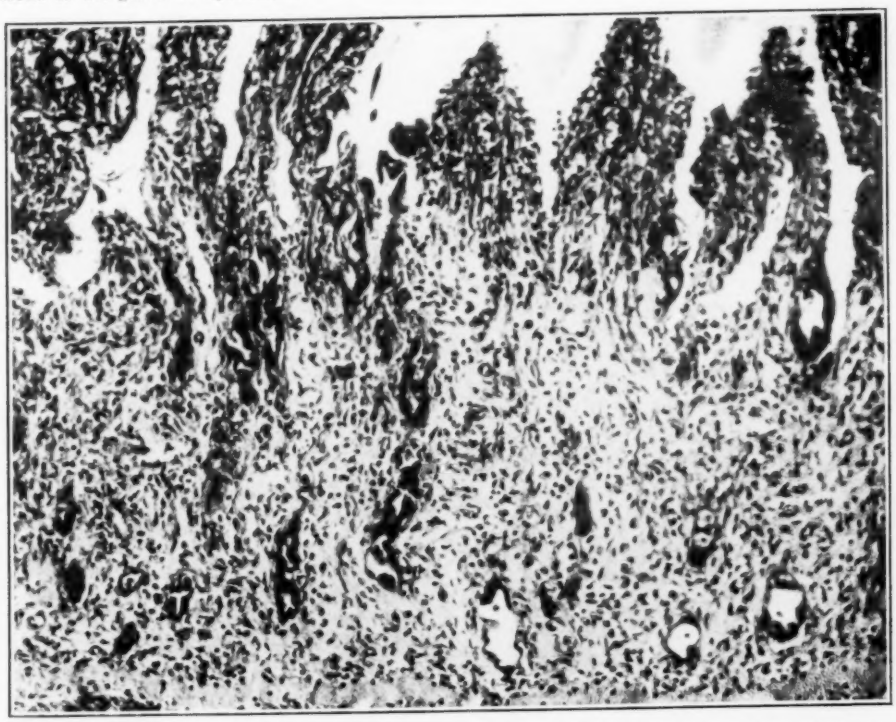

Fig. 10.—Same dog as preceding. Middle portion of small intestine showing desquamation of the superficial epithelium and necrosis of the epithelium of the glands of Lieberkühn. Severe enteritis.

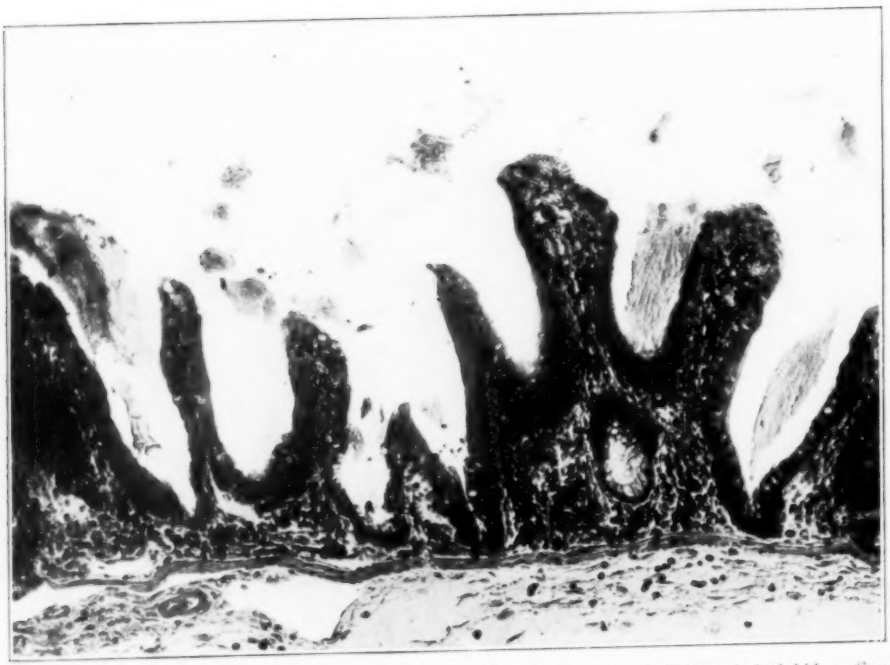

Fig. 11.—Rabbit 63. Received subcutaneous injection of .06 c.c. of dichlorethylsulphide. Severe diarrhea from fourth to ninth day. Killed fifteen days after injection. Mucosa of intestine intensely congested and edematous. Marked mucoid degeneration with cystic glands. Regeneration of superficial epithelium.

Fig. 12.—Rabbit 50. Received subcutaneous injection of .06 c.c. of dichlorethylsulphide. Very severe diarrhea on fifth to seventh day afterwards. Apparent recovery. Killed on the thirty-second day after injection. Mucosa shows excessive mucus formation.

of the whole splanchnic area, with edema, and occasional petechial hemorrhages and minute erosions of the mucosa. Degenerative changes have also been noted in the epithelium of the bile ducts, and the postmortem changes in the mucosa of the gall bladder and larger bile ducts appear to be greatly hastened, and more severe than normal, as though from the presence of some necrosing substance in the bile. (See Figs. 4 to 13.) A very striking feature of the pathology of many cases of subcutaneous injections of dichlorethylsulphide is the presence in the blood spaces and sinusoids of the spleen of great numbers of large pigmented phagocytes and hemophages containing altered red blood cells, indicating a greatly increased hemolysis. (See Fig. 13.)

The microscopic appearances of the tissues at the site of injection are those

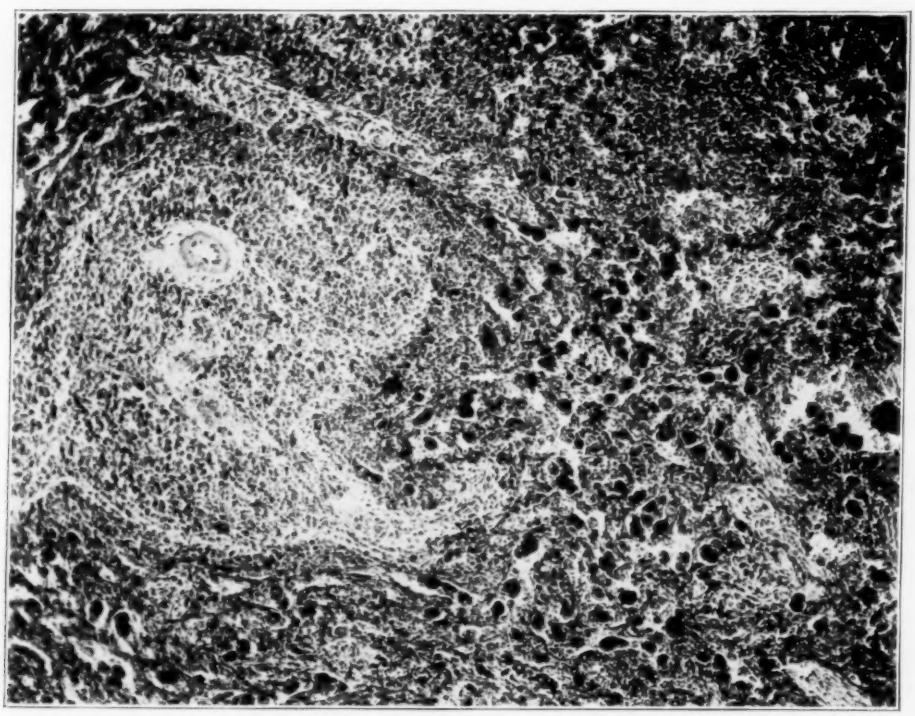

Fig. 13.—Rabbit 47. Received subcutaneous injection of .03 c.c. of dichlorethylsulphide. Very severe diarrhea on fourth to eighth day. Died on twelfth day after injection. Intestines showed severe catarrhal enteritis. Section of spleen showing the great number of pigmented phagocytes in the blood sinuses.

of an extensive eschar extending entirely through the skin and fascia, and deep into the muscles with extensive extravasations and infiltrations of leucocytes. The appearances of secondary infection are frequently added to those of the primary lesion. In several instances deposits of lime salts were noted in the necrotic area.

Intravenous Injections.—When dichlorethylsulphide is injected directly into the external jugular or superficial femoral veins in doses varying from .0075 to .18 c.c., the animal shows no signs of pain and returns to eating, but within a short time begins to show symptoms of hyperexcitability in the form of very

rapid respiration and slight convulsive movements. Within an hour there may be general convulsions and opisthotonos with head turned to one side. The animal quickly becomes very weak, tends to lie upon its side with rapid jerking movements of the legs, as though running. The animal can not turn over. Soft feces are frequently involuntarily discharged. The animal acts as though nauseated and there are slight salivation and lacrimation. The pupils are dilated. The temperature rapidly falls six to eight degrees before death. The convulsions cease, the pupils contract, salivation increases, the animal passes into coma, and there is a gradual failure of circulation and respiration, although the respiration ceases some time before the heart stops beating. Death usually takes place in one to four hours, depending upon the size of the dose. Following the intravenous injection of larger doses, the first convulsive movements may appear in ten minutes and be followed rapidly by wild clonic convulsions, very much resembling those of rabies.

The gross pathologic changes following intravenous injections of dichlorethylsulphide are dilatation of the heart, particularly on the right side, and marked congestion of the lungs with numerous petechial hemorrhages. All other organs show congestion with numerous minute hemorrhages. Mucosa of gastrointestinal tract is covered with thick mucus, is congested, and may show minute hemorrhages. The contents of the gall bladder may be a thin and pale bile. No specific changes were found in the brain and cord and no thrombus in the vein at the site of injection.

Microscopic examination confirms the gross appearances, in that it shows extreme congestion, stasis and hemorrhages in the lungs; congestion of the gastrointestinal tract, with an increased formation of mucus scattered irregularly throughout, not comparable, however, to the changes found in animals injected subcutaneously; and marked general congestion.

EPICRISIS

The introduction of dichlorethylsulphide into the blood stream causes death within a few hours with characteristic symptoms. When injected subcutaneously, with resulting slower absorption into the circulation, death occurs later, from twelve hours to several days, likewise with a characteristic symptomatology. The symptoms may be classed roughly as (1) nervous and (2) intestinal. In the case of large doses, with death occurring within an hour, the nervous symptoms may alone be exhibited, while in the animals living for some time the nervous symptoms are slight and those of the intestinal group predominate. In the correlation of the pathologic findings with the symptomatology, no change has been found in the central nervous system offering an adequate explanation for a death dependent entirely upon a lesion of the central nervous system. In the delayed cases (subcutaneous) the intestinal tract offers a pathologic picture commensurate with the symptoms. In addition to the specific pathology just mentioned, incidental pathologic findings in the form of thrombi, emboli, embolic infarctions and hemorrhages may at times be interpreted as explaining some of the observed clinical phenomena.

Of all the pathologic lesions produced by mustard gas, apparently the most specific and most interesting are the intestinal changes following intravenous and subcutaneous injections. The intense catarrhal enteritis observed after such injections suggests the excretion of dichlorethylsulphide or some product of its decomposition through the intestinal mucosa. No changes have ever been observed in the kidneys, indicating the excretion of any toxic product through the renal epithelium. In the case of the liver there have been observed, at times, degenerative changes in the biliary epithelium, suggesting the presence of some injurious substance in the bile. Further, the probability of this hypothesis seems the greater in view of certain changes, found in a certain proportion of cases, in the gall bladder, in the form of an apparently earlier postmortem necrosis of the gall bladder wall, and a diffusion of the bile into the neighboring liver tissue. It has been a notable observation that, in many cases, when autopsy was performed immediately upon death of the animal, such early postmortem change was found in the gall bladder; while in animals that had not received dichlorethylsulphide injections, such an immediate postmortem change was not observed.

A large number of experiments were made in the effort to demonstrate the presence of mustard gas or its products in the intestinal wall and contents, and in the liver and bile. In the tissues at the site of the injection, the odor of mustard gas will persist for several days and cutaneous applications of the ether extract of these tissues will produce a well-marked mustard burn, even when the ether extract is much diluted. Further, in one case in which death occurred within one hour after jugular injection, with numerous small embolic hemorrhages in the lungs, the odor of mustard gas was clearly evident on section of the lung, and an ether extract of the lung gave a slight positive test. With this single exception we have been unable to obtain any odor of mustard gas or any positive skin reaction from extracts of any organ. Ether and aqueous extracts of the liver and bile, the intestinal tract and its contents, the blood, heart and lungs, and of the urine, even when concentrated, have yielded no odor of mustard gas and have given no positive skin test.

It has been generally assumed that the injurious action of mustard gas follows its hydrolysis in the living cells and tissues. The products resulting from the hydrolysis of dichlorethylsulphide are hydrochloric acid and dihydroxyethylsulphide.

From Major Moses Gomberg of the Chemistry Department of the University of Michigan a quantity of pure dihydroxyethylsulphide was obtained. Varying series of experiments made with this substance showed it to be apparently inert, both as applied locally, by ingestion, and by subcutaneous and intravenous injections, in quantities up to many times the lethal doses for dichlorethylsulphide. No diarrhea, no fall in temperature, and no other symptoms were produced, and no pathologic lesions were found in such animals with the exception of marked fatty changes in the liver cells.

A similar set of experiments with hydrochloric acid injections was also carried out. The subcutaneous injection of hydrochloric acid, even in a dose

of .12 c.c. produces intense local irritation and pain, in striking contrast to the anesthetic action of dichlorethylsulphide. The course of the local lesion is entirely unlike that produced by mustard gas. The liquefaction of the eschar is very rapid and there quickly results a deep excavated lesion, the bottom and sides of which appear charred. (See Fig. 3.) No diarrhea is produced; the temperature remains normal or rises; no systemic symptoms are produced, and the animal will recover unless secondary infection sets in.

The intravenous injection of .06 c.c. of hydrochloric acid (diluted to prevent local injury during injection) produces no symptoms comparable to those resulting from the intravenous injection of dichlorethylsulphide.

The manner of causation of the intestinal lesions remains the special problem of the pathology of dichlorethylsulphide poisoning. Neither hydrochloric acid nor dihydroxyethylsulphide, when introduced into the circulation, will cause similar changes. Therefore these lesions can not be the result of the action of hydrochloric acid produced at the site of the lesion and circulating in the blood. The next most plausible explanation of the cause of the intestinal lesions is that mustard gas itself or some other unknown decomposition product circulates in the blood and is excreted through the mucosa of the intestine, or possibly, also, through the bile.

It has been stated that the most delicate chemical test for mustard gas is a color reaction with a solution of platinic chloride and sodium iodide. The liquid to be tested is applied to absorbent paper moistened with this solution. In the presence of dichlorethylsulphide the pink color is changed to a faint purple, which becomes blue or deep blue, depending upon the concentration of the mustard gas solution. When this test was applied to ether and aqueous extracts of the liver, bile and intestine from animals injected subcutaneously and intravenously with dichlorethylsulphide, we obtained a definite blue color more marked in the case of the aqueous extracts. This reaction we at first believed to be a positive test for mustard gas in these extracts. Continuing our control experiments, we found that the dihydroxyethylsulphide gives the same reaction with the platinic chloride-sodium iodide as dichlorethylsulphide. The test is, therefore, not a specific one for pure dichlorethylsulphide. We then took the aqueous extracts of liver, bile, intestine and urine, which might be expected to have the dihydroxyethylsulphide in them, if it were present at all, since it is soluble in water, and heated them with concentrated hydrochloric acid with the expectation of reconverting the hydrolyzed product into mustard gas. The products thus obtained, however, gave no odor of mustard gas, and their ether extracts neither gave a skin reaction nor a positive color test. On the other hand, these aqueous extracts of body fluids and organs did give bluish green color tests with the test solution that might be interpreted as faint positive reactions for mustard gas. Unfortunately, however, the aqueous extracts of these same organs and fluids from animals untreated with mustard gas produce an identical color reaction. We have, therefore, been unable to demonstrate the presence of mustard gas or its hydrolyzed products in the liver, bile, intestines, feces, blood or urine.

CONCLUSIONS

1. Dichlorethylsulphide when injected internally in doses of approximately .06 c.c. per kilo for the rabbit, and .03 c.c. per kilo for the dog, causes a fatal intoxication, characterized, when death occurs quickly, by symptoms referable to the central nervous system; but when death takes place more slowly, by intense diarrhea, anorexia and reduction of temperature.

2. The only specific pathology of such fatal poisonings is a marked degeneration of the epithelium of the gastrointestinal tract in the form of a severe catarrhal enteritis, and the occasional occurrence of similar changes in the epithelium of the bile ducts and gall bladder.

3. These changes suggest the excretion of mustard gas or some poisonous product resulting from its decomposition into the gastrointestinal tract. No positive proof, however, of this mode of excretion could be obtained. The hydrolysis of mustard gas circulating in the blood may take place in the intestinal mucosa, thereby producing the degenerative changes seen in these cells. On the other hand, the intestinal conditions may not be due to the direct action of any substance upon the epithelium of the mucosa, but may be secondary to the splanchnic congestion and the hyperexcitability of the nervous centers.

4. It seems probable that the characteristic symptoms and death following subcutaneous and intravenous injections of dichlorethylsulphide are due to the direct action of this substance circulating in the blood, upon the central nervous system, either with or without hydrolysis in the nervous tissue affected. The specific character and constancy of the symptomatology offer sufficient argument against any assumption that the process is embolic in character.

IV. SUSCEPTIBILITY

In Meyer's first laboratory experiments with dichlorethylsulphide he noticed an apparent difference in individual susceptibility, in that he, himself, was not affected by exposure to it, while a laboratory worker engaged in making it developed conjunctivitis and a severe skin eruption. Meyer's conclusion that individual susceptibility must vary greatly seems hardly warranted by this observation. Undoubtedly Meyer was working with a very impure compound, the concentration of which must have varied from time to time, and the laboratory worker must have been much more exposed to its fumes than Meyer, himself. Further, the dissemination of mustard gas is such an insidious matter of physical conditions and pure chance, that in a group of workers exposed to apparently identical conditions the greatest diversity of effects may be produced, leading to an incorrect supposition of especial resistance or susceptibility in the individual members of the same group. The question of the existence of individual susceptibility can, therefore, be settled, only by the application of experimental methods in which the conditions of exposure are identical.

This has been done by *Marshall, Lynch, Smith,* and *Williams* (Medical Division, Chemical Warfare Service Reports, Nos. 288, 290, 302, 303, 320). These workers found that the results of uniform skin tests showed that there does exist a decided individual difference in the skin reaction to mustard gas

independent of changes in sensitivity due to sweating, etc. About 20-40 per cent of the white men tested showed a certain degree of resistance; while 78 per cent of negroes tested showed a similar resistance. About 2 per cent of the white individuals showed a hypersensitivity; no hypersensitive cases were found among negroes. There exists, then, a much greater degree of cutaneous sensitivity to mustard gas among white people than in the colored race. Groups of individuals treated at different times do not show any great change in sensitivity from time to time. In Report 316, *Marshall, Miller, Reed* and *Beaver* state that in the gassing chamber very little difference in susceptibility has been noted in the dog, monkey, goat, rabbit, guinea pig, and mouse. So far as the conjunctiva and respiratory mucous membrane is concerned there appears to be little or no variation in individual sensitivity. In Report 328, *Marshall* and *Williams* in a study of sensitivity in different animals in their reaction to the skin test found the horse most sensitive and monkeys most resistant, the dog most closely approaching man in percentage of reaction. Individual differences in sensitivity were also noted in animals. An acquired hypersensitivity to mustard gas vapor as the result of previous or repeated burns is claimed by many workers, and accepted by some observers. That such a localized susceptibility may be shown in scars, healing burns, injured conjunctiva and mucous membranes, is very probable, but there is no evidence to the effect that exposures to mustard gas increase the individual's susceptibility on the part of the whole organism.

The individual human sensitivity is in part a racial one, and, therefore, intrinsic and constitutional. *Marshall* (Chemical Warfare Service Reports) would explain it as due to differences in the skin, cutaneous lipoids, etc. Among the individuals of the same race showing differences in cutaneous sensitivity to mustard gas he noted no other constitutional differences or peculiarities. In the cases seen by us there were five individuals who seemed to be cutaneously hypersensitive, as shown by their receiving frequent and severe burns from vapor exposures not affecting other workers so severely, although apparently similarly exposed. The two fatal cases belonged to this group. It is noteworthy that all five of these cases presented constitutional stigmata or clinical symptoms of a definite pathologic constitution, the *thymicolymphatic*.

Autopsy on one case showed a persistent thymus and characteristic lymphoid hyperplasia with exhaustion of the germ centers. The fact that individuals possessing this constitution are especially susceptible to skin conditions, such as eczema, to food idiosyncrasies, to asthma and pollen intoxications, to death from anesthesia, slight surgical operations, slight thermal burns, etc., and to death from acute infections, makes it very probable that a large number of the hypersensitive to mustard gas may possess this constitution. As its chief features can be easily recognized by a good clinician, and as many of its features can be brought out by the clinical history, all workers in mustard gas should be subjected to an examination for the existence of this constitution, and those possessing it should be rejected.

The chief objective features of the constitution are a short, full neck, rounded thighs and hips, evidences of rachitis, pasty or pale complexion, ten-

dency to mouth breathing, adenoids and enlarged tonsils, palpable lymph nodes. Occasionally these features are combined with the tuberculous habitus, long narrow flat thorax, floating ribs, long belly, low scrotum, etc.

In the clinical history the following points should be noted: tendency to croup, laryngeal stridor, asthma, hay fever, unusual tendency to bronchitis, severe reaction to acute infectious diseases, food and drug idiosyncrasies (lobster, crab, egg, honey, strawberries, raspberries, milk, cocoa, tea, morphine, chloroform, quinine, etc.),severe serum reactions, severe anaphylactic phenomena, tendency to eczematous conditions of the skin, goiter, tendency to faint on slight cause, sensitiveness to shock. At autopsy enlarged thymus and hyperplastic lymph nodes are found.

The determination of this constitution is not difficult; and an investigation should be made as to its frequency in those individuals hypersensitive to mustard gas.

FINAL SUMMARY OF DICHLORETHYLSULPHIDE INVESTIGATION

This paper, the sixth in number, closes the series of investigations on dichlorethylsulphide carried out during the last year in the Pathological Laboratory of the University of Michigan. Begun as an independent war research problem, the laboratory later, through Dr. Warthin, became associated with the Medical Advisory Board of the Chemical Warfare Service, and abstracts and preliminary reports of these investigations are included in the Reports of that service. All of the articles have been published in full in this Journal (*Pathology of the Skin Lesions*, May, 1918; *Pathology of the Ocular Lesions*, October, 1918; *The Treatment of Dichlorethylsulphide Injuries*, ibid.; *The Clinical Pathology of Dichlorethylsulphide Poisoning*, November, 1918; *Lesions of the Respiratory and Gastrointestinal Tracts*, this number). In this, the final article, it seems advisable to assemble the main points of knowledge gained by the investigation in the form of the summary given below. The research, which has been carried out in a most intensive manner, involving an immense amount of labor, has been made possible only through the enthusiastic cooperation of the entire laboratory staff, and to these, especially to Dr. Harriet Taylor, we wish to give appreciative thanks. To Major Moses Gomberg, Professor of Chemistry in the University of Michigan, we owe, first of all, our opportunity to take up this research, inasmuch as he, in the beginning, furnished us with a quantity of the purest mustard gas we have been able to obtain from any source. With the dichlorethylsulphide made by him, an absolutely colorless liquid possessing but a faint odor, we have been able to standardize our entire series of investigations; at the same time we have compared its results with those of other samples less pure, obtained from the Chemical Warfare Service and elsewhere. To Dr. Gomberg we owe thanks also for a quantity of pure dihydroxyethylsulphide. To the Regents of the University of Michigan we are also indebted for a special grant of funds for necessary expenditures for animals and additional technical assistants. Finally, to Miss Frances Dunbar, we wish to give our thanks for her care and skill in printing our photomicrographic plates.

SUMMARY

I. *Dichlorethylsulphide* (*"Mustard Gas"*), in liquid or in vapor form, even in very low concentrations, is an escharotic poison for the animal tissues (skin, conjunctivæ, cornea, mucous membranes of respiratory and gastrointestinal tracts) with which it comes in direct contact. The degree of the injury is proportionate to the concentration of the gas, the time of exposure, individual susceptibility, and local physical conditions, such as moisture, sweating, warmth, pressure and friction. The escharotic action is, for the greater part, painless, the anesthetic effect being especially notable upon the skin; while upon the mucous membranes its action may be more irritant, probably chiefly reflex in character. The cutaneous surfaces most susceptible are those with thinner, more delicate skin, well supplied with sweat glands and hair follicles, where sweat may collect, and which are exposed to friction or pressure, such as the axillæ, flexor surfaces, genitals, inner surface of arms and corresponding surface of trunk, inner surfaces of thighs, between the fingers, etc. There is a penetration of the gas into the sweat and sebaceous glands. The injuries are particularly striking in their insidious, slowly progressive development, becoming first apparent only some hours after the exposure. Upon human skin the lesion appears as a hyperemia, followed by vesication, eschar formation, sloughing, and slow healing, with more or less pigmentation. Depilation may occur; in severe cases the eschar may extend entirely through the corium into the subcutaneous tissues. Secondary infection and gangrene of the eschars occurs invariably in cases not properly treated. Milder lesions may show only the earlier stages of hyperemia, vesication or pigmentation. In general the injuries may be classed as burns of first, second, or third degree. Following extensive hyperemias in human skin a most marked pigmentation, exceeding in degree the most marked forms of solar tan may be quickly developed and fade slowly. This pigmentation may be diffuse or spotted. In human skin vesication is pronounced; in animals the cutaneous lesions are characterized by the development of marked subcutaneous edema in the injured area. The fluid of the vesicle or of the edema is nonirritating when applied to uninjured areas. In the case of human skin frequently exposed to very dilute concentrations (only perceptible by odor), an eczematous itching condition between the fingers, on the genitals, etc., may develop; rubbing or scratching of the itching part may lead to the quick development of a blister or superficial eschar. Such interdigital lesions in laboratory workers may resemble clinically those produced by the itch mite. Cutaneous areas injured by mustard gas are rendered more susceptible to trauma or other forms of injury, including new exposures to mustard gas. This local susceptibility is, however, a general one, and not a specific lowered resistance to the action of dichlorethylsulphide. Subcutaneous injections of pure dichlorethylsulphide produce painless eschars, followed by dry sloughing, with edema less marked than in the case of external cutaneous application; a hypostatic edema may develop on the animal's belly when injected in the back. In the tissues at the site of the injection and in the hypostatic edema mustard gas may be present for some days after the injection. The resolution of mild

skin injuries is often attended by troublesome itching. Healing of the deep cutaneous eschars is very slow; large scars may be produced resembling those resulting from deep thermal burns. The hairs may be lost; but when regenerated they may be white in color.

Upon the cornea mustard gas exerts an especially injurious action, particularly at the vertex. Within ten to fifteen minutes after exposure to dilute concentrations, degeneration or necrosis of the corneal surface may be demonstrated by the application of a 2 per cent alkaline aqueous solution of fluorescein, the injured cells retaining a greenish fluorescent coloration. In more severe injuries the cornea may be killed throughout its entire thickness at the vertex. The mildest cases show a slight cloudiness; the severe cases present a characteristic porcelain appearance of bluish white opalescent cloudiness, often with a more opaque band or line running horizontally across the cornea just below its transverse diameter. The injury to the conjunctiva is shown by the development of a more or less severe catarrhal, seropurulent or purulent conjunctivitis with marked edema of the subconjunctival tissues leading often to "ruffling" of the lids, entropion, ectropion, or a combination of these. Even the lighter cases tend to run a chronic course with disturbances and reduction of vision. In the severe cases cicatrization and vascularization of the cornea take place slowly with resulting impairment or loss of vision. The injured eye is more susceptible to infection; and in infected cases suppurative panophthalmitis may develop with complete destruction of the eyeball. Recovered cases of mild mustard gas conjunctivitis often show an increased sensitivity to the action of light, dust, and other irritants, including mustard gas fumes.

Upon the mucosa of the respiratory tract mustard gas vapor produces a local injury to the epithelium as shown by the development of a catarrhal, desquamative, membranous, diphtheritic or purulent inflammation (rhinitis, stomatitis, pharyngitis, laryngitis, tracheitis and bronchitis), these lesions being most severe in the nose, back of tongue, palate, pharynx and larynx, decreasing in intensity downwards. Coryza, salivation, dryness of mouth and throat, aphonia and persistent cough are the chief symptoms, with physical signs of laryngeal, tracheal and bronchial involvement, and atelectasis and edema of the lungs. As a result of secondary infection a purulent bronchopneumonia may develop.

Through the swallowing of air, saliva or secretions from the upper respiratory tract containing mustard gas, or from the ingestion of contaminated food local corrosive action upon the alimentary mucosa may be produced, varying from a catarrhal inflammation to large areas of eschar formation with resulting gastric ulcer, perforation, etc. The symptomatology of the mildest lesions is covered up by that resulting from the more severe burns elsewhere; the more severe ones will produce marked symptoms referable to the stomach and intestines.

II. There exists a racial and an individual susceptibility to the action of dichlorethylsulphide, particularly in the case of the skin, and probably also in the respiratory tract. The individual susceptibility, in some cases at least, is

associated with the constitutional stigmata and symptomatology of the thymicolymphatic constitution. Acquired susceptibility is not specific.

There is no evidence of any systemic poisoning by the absorption of dichlorethylsulphide from the skin, eyes or mucous membranes of the respiratory or gastrointestinal tracts. There is no metastatic action of the gas from the site of local external application.

In all severe cases of mustard gas burns of skin, eyes, or mucous membranes there is usually the clinical picture of severe shock, in the form of intense pallor, depression of pulse and temperature, general collapse, nausea and vomiting. The mildest cases show no systemic reaction.

No changes are observable in the blood or urine of mild cases. In cases with large infected burns of skin or respiratory tract, the blood presents a mild secondary anemia with leucocytosis; the blood urea is increased; the urine is diminished, concentrated, and contains casts and albumin. Under forced fluids the urinary symptoms improve, and the blood urea diminishes. In severe infected cases the general picture may be that of a severe toxemia.

When injected intravenously or subcutaneously dichlorethylsulphide is an active poison, causing death in one to four hours intravenously and two hours to three weeks after subcutaneous injections (for rabbits intravenous injections of .0075 c.c. per kilo may be lethal within four hours), according to size of dose, individual animal, etc. When death takes place quickly, the symptoms are chiefly those of an action upon the central nervous system, such as hyperexcitability, rapid respirations, general convulsions, opisthotonos, gradual failure of respiration and circulation, coma and death. When the animal lives longer after small intravenous injections, or after subcutaneous injection, there develops a characteristic symptomatology of salivation, marked diarrhea, and fall of temperature, with marked anorexia, emaciation and depression. With subcutaneous injections of .015 to .06 c.c., death usually takes place from the fourth to the tenth day.

III. The specific microscopic pathology of the local lesions of dichlorethylsulphide poisoning consists in degeneration and necrosis of the cells with which it comes in contact. The earliest microscopic change is pyknosis of the nucleus and cell body, followed by hydropic degeneration, liquefaction or coagulation necrosis. In the skin, hyperemia, with regeneration of the damaged cells, vesicle formation, desquamation of the dead epidermis or eschar formation mark varying stages of severity of the lesion. The degenerative changes extend deepest in the hair follicles and sweat glands. In severe burns the necrosis may extend entirely through the corium. In the cornea, pyknosis and simple or coagulation necrosis of the corneal epithelium and interstitial substance, even to the endothelial layer, in extent varying with the degree of exposure, constitute the microscopic features. On the conjunctivæ the epithelium shows pyknosis, hydropic degeneration, liquefaction necrosis, or there may be a deeper necrosis extending into the subconjunctival tissues. The conjunctival surface suffers to a less degree proportionately than the epidermis. On the mucous membranes the epithelium shows pyknosis, hydropic or mucoid degeneration, desquamation, liquefaction or coagulation necrosis. The necrosis

may extend into the submucosa, but the depth of the lesions on the conjunctivæ and the mucous membranes of the respiratory tract is never so great from identical exposures, as it is in the skin. Following the necrosis there is marked hyperemia, and the development of an edema, more marked in the subcutaneous and subconjunctival tissues in animals, but less marked in man. The blood vessels in the necrotic area are killed, the blood cells hemolyzed without thrombus formation or much extravasation, except minute hemorrhages by diapedesis. Following the lesion there is a demarcating inflammation, with slow regeneration, repair or cicatrization. On the mucous membranes there results in the severe cases a localized eschar or ulcer, or a more diffuse diphtheritis. With secondary infection the inflammatory process becomes purulent or suppurative. The influence of secondary trauma and infection is well shown in the early development of deep areas of decubitus in the injured regions of the skin. Multiple furuncles may develop, or large cutaneous areas become gangrenous. In the eye purulent involvement of the anterior chamber, iris and ciliary body may occur, or even a suppurative panophthalmitis. In the respiratory tract secondary infection of the injured mucosa may lead to a purulent bronchopneumonia.

The internal organs in animals with mustard gas lesions of the skin, eyes, respiratory or gastrointestinal tract offer nothing of a specific pathologic nature. There is general congestion, marked splanchnic congestion, acute catarrh of the intestines and, in infected cases, some cloudy swelling of the kidneys.

In fatal cases the cause of death is to be found in shock, secondary infection with toxemia, or local conditions as laryngitis, tracheitis, bronchitis and bronchopneumonia. It is also possible that the entrance into the body of shell fragments carrying liquid dichlorethylsulphide might cause a relatively speedy death through absorption.

At the site of subcutaneous injections there is found a local eschar with demarcating hemorrhage, edema and inflammatory infiltration; in the large veins into which injections have been made, no changes have been found except occasional thrombosis.

The general pathology of the injected cases presents a specific pathologic picture in the intestinal tract in the form of a severe mucoid, desquamative or necrotic enteritis, the intestinal epithelium showing the most marked hydropic or mucoid degeneration, even to liquefaction necrosis. Similar changes may be found in the epithelium of the bile ducts. In the other organs no pathologic changes but congestion have been found, with the rare exception of emboli or thrombi.

IV. The cause of death in intravenous and subcutaneous injections would appear to be the direct action of minute quantities of free dichlorethylsulphide or some poisonous product resulting from its decomposition, upon the cells of the central nervous system. It has been assumed that the pathologic action of dichlorethylsulphide is due to its hydrolysis within the tissue cells. The products of this hydrolysis, hydrochloric acid and dihydroxyethylsulphide, when injected into the blood, do not produce the same effects. Dihydroxyethylsulphide and hydrochloric acid, when injected into the circulation in much

larger doses than would result from the hydrolysis of the fatal doses of mustard gas, are harmless. The effect upon the cells of the central nervous system may, however, depend upon the hydrolysis in these cells of minute quantities of mustard gas in the circulation, or these cells may be injured without such hydrolysis occurring. It is probable that the gastrointestinal catarrh resulting from the injections of dichlorethylsulphide is secondary to the nervous injury, rather than to an excretion of the poison or poisonous products through this tract. No positive tests for dichlorethylsulphide or dihydroxyethylsulphide have been obtained in the bile, intestinal contents, or urine. Incidentally, it has been shown that the platinic chloride-sodium iodide color test for dichlorethylsulphide is not applicable to the body fluids or extracts of various organs and tissues, as similar color changes are produced by some of these.

V. The principles of treatment to be applied to mustard gas injuries are primarily those that will remove any of the gas remaining, prevent infection, and promote healing. Our experience leads us to recommend the use of Dakin's solution in irrigation or full baths for the skin lesions, and a 0.5 per cent solution of dichloramine-T for the eye lesions, and also as a mouth wash. The fluid intake should be forced when the urine is concentrated. Pressure must be removed from all injured areas. Air-excluding and infection-including protections, such as oily dressings, paraffin sprays and coatings, zinc stearate, olive oil, vaseline, etc., should not be used, unless there is an active and persistent germicidal agent present as in the case of sodium stearate impregnated with chloramine-T, or the chlorcosane solution of dichloramine-T.

VI. As to its use in warfare, mustard gas is a disabling rather than a killing agent. Under the actual conditions of the field the great majority of mustard gas casualties are likely to be of a nature tending to incapacitate the injured for service for a number of days or weeks, or even for months. Added to this, the insidious character of this invisible fire, painless and often unrecognized in its action, makes mustard gas a potent factor in undermining the morale of the troops exposed to it.

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EDITORIALS

Influenza and Pneumonia at Camp Grant

CAPTAIN Edwin F. Hirsch and Technician Marion McKinney have made a most thorough study of the influenza epidemic at Camp Grant. They close their report with the following summary:

1. An epidemic of unusual virulence swept with great rapidity through several organizations in Camp Grant between September 21, 1918, and October 18, 1918. During this time 9,037 patients were admitted to the Base Hospital, representing about one-fourth of the strength of the camp, and of these, 26 per cent developed pneumonia. About 11 per cent of the total admissions, or 43 per cent of the total cases of pneumonia died.

2. From the throat cultures of the early admissions pneumococci were recovered with remarkable constancy, influenza bacilli were found exceptionally.

3. Postmortem examinations of those dying during the epidemic demonstrated with great regularity a massive bronchopneumonia.

4. In cultures of the diseased lung, heart's blood, exudates, fluids, and other diseased foci of the body, pneumococci were the predominating organisms.

5. In 50 per cent of the cases of pneumonia, blood cultures demonstrated the presence of pneumococci unmixed with other organisms.

6. Pneumococci in pure culture were recovered from infected sinuses of the head, middle ears, conjuctival and empyema exudates.

7. Experimental inoculation of pneumococci isolated during the epidemic into laboratory animals, demonstrated an exceedingly great virulence for these organisms.

8. Control throat cultures made from German prisoners in the camp, but who escaped the epidemic, showed no pathogenic organisms.

9. The number of German prisoners whose throats were cultured was fifty, and in 50 per cent of these pneumococci were found, but in only three did this organism prove pathogenic to laboratory animals.

10. All strains of pneumococci isolated during the epidemic were tested for their virulence in white mice. Minimal quantities of 24-hour cultures were found highly lethal in susceptible animals. Comparatively small fractions of 24-hour blood agar slant cultures were fatal to rabbits and guinea pigs. The virulence of these strains is considered sufficient to account for the epidemic.

11. One hundred ninety-eight autopsies studied bacteriologically gave the following results:

(a) In the Lungs:	
Pneumococcus pure	89
Pneumococcus and other organisms	55
Hemolytic streptococcus	19
Other organisms	4
Unsatisfactory and not cultured	31
Total	198
(b) In the Heart's Blood:	
Pneumococcus pure	53
Hemolytic streptococcus	23
Pneumococcus and hemolytic streptococcus	1
Other organisms	2
Negative	109
Not taken	10
Total	198

12. The types of pneumonia were distributed as follows:

Type	Number	Per cent
(a) In the Heart's Blood:		
I	5	7.46
II	45	67.16
IV	17	25.37
(b) In the Lungs:		
I	12	6.
II	109	54.2
III	2	1.
IV	78	38.8
(c) In the Spinal Fluid:		
I	3	25.
II	7	58.3
IV	2	16.7

13. The following are the gross pathologic changes found in autopsy:

(a) Extensive bronchopneumonia.
(b) Slight serofibrinous pleuritis.
(c) Acute catarrhal bronchitis and tracheitis.
(d) Acute hyperplasia of the spleen, parabronchial, mesenteric and biliary lymph glands.
(e) Marked cloudy swelling of the myocardium and the parenchymatous organs.
(f) Marked loss of the yellow of the adrenal cortices.
(g) Acute fatty changes of the liver and kidneys.
(h) Multiple petechial hemorrhages of the serous surfaces.
(i) Jaundice.
(j) Acute catarrhal conjunctivitis.
(k) Slight acute serous pericarditis.
(l) Moderate generalized passive hyperemia.

14. In one hundred ninety-eight autopsies, the lobes involved were as follows:

(a) Left lower	149
(b) Right lower	141
(c) Left upper	83
(d) Right upper	119
(e) Right middle	81

—*V. C. V.*

Notes on Influenza

INFLUENCE of Length of Service.—The fatality of the epidemic was greater among those recently brought into the service. This is illustrated by the following abstract taken from a report made by Lieut. Wilson D. Wallis at Camp Lee. This report shows that while those who had been in the service less than one month constituted only 9.19 per cent of the total strength, they furnished 30.11 per cent of the total deaths from influenza and consequent pneumonia. Furthermore, it is shown that while those who had been in the service from one to three months constituted 45.18 per cent of the camp, they furnished 46.24 per cent of deaths. On the other hand, those who had been in the service more than three months constituted 45.63 per cent of the population and furnished only 23.69 per cent of deaths.

Lieut. Wallis says:

"These figures show a much greater percentage of deaths for the first month in camp than the corresponding proportion of the population would warrant; while in the period of three months or more of service, the percentage is less than half of that of the camp population having this length of service. The only approach to a correspondence is in the period from one to three months where the respective percentages differ but little. The increase in length of service is accompanied by a progressive decrease in the percentage of deaths from 30.11 per cent to 27.41 per cent to 18.87 per cent, although only 9.19 per cent of the population in the camp falls within the class of less than one month's service.

"The incidence of mortality is in the first month's service more than three-

fold the percentage of the number of men; and in the period of three months or more of service is scarcely more than half of the percentage of the number of men of the camp in that group."

The fact that the case mortality is higher among those who came from rural homes than among those who came from cities, seems to hold even after three months of service, or more.

The 34th Division which was then in camp at Cody during the preceding Winter and Spring was in Camp Dix, New Jersey, when the epidemic broke out in September, 1918. This Division was composed of fairly well-seasoned men, but the death rate in the Division was 18.70 per cent per thousand as compared with that of 17.21 of men from the 811th Pioneer Infantry composed largely of those fitted only for limited service. It is suggested by the officer making the report that this is due to the fact that such a large proportion of the 34th Division came from rural districts.

The case fatality at Camp Dix among those who came from cities with a population of 10,000 or more, was 10.8; while among those who came from more rural homes the rate was 15.8, although the average service of both groups was the same.

Clinical Features.—The clinical features as described by Majors Synnott and Clark of Camp Dix may be abstracted as follows:

"The usual history was one of gradual onset with prodromes for four or five days prior to admissions,—consisting of headache, malaise, backache, myalgia, fever and chills or chilly sensations, and marked prostration. There was a history of anorexia, and of aggravation of symptoms, after drill or exercise. Occasionally the onset was sudden, sharp and severe. On admission there was cough, often with rusty sputum, a temperature of 103° F., occasionally hyperpyrexia, respirations of 28 to 30, pulse between 80 and 120, a low temperature in a severe case was an unfavorable sign. The blood count showed usually leucopenia. The urine contained albumin and casts. The patients looked very sick, but often did not feel so. Few complained of sore throat or the early sticking pains in chest, aggravated by coughing, so commonly observed in beginning pneumonia.

"The outstanding feature of the disease was the extreme toxemia noted in the serious cases. We could predict almost from the first inspection the outcome of each case. There has been a sharp line of demarcation between the serious and mild cases. Many of the former developed a cyanosis early in the disease and died promptly, after periods varying from a few hours to three days after admission.

"The cyanosis appeared early and was progressive. It was a fairly constant and characteristic symptom in the severe cases. This intense cyanosis was a striking phenomenon. The lips, ears, nose, cheeks, tongue, conjunctivæ, fingers, and sometimes the entire body partook of a dusky, leaden hue. Frequently this cyanosis was apparent before there were any demonstrable physical signs of pneumonia. The cause could not be ascertained, a few spectroscopic readings failing to show absorption bands of methemoglobin. As autopsy revealed marked so-called compensatory emphysema in these cases and as cyanosis is a

common accompaniment of emphysema, possibly this was in some wise accountable for the condition.

"The disparity between temperature and pulse was striking. Patients with temperature between 104° and 106° not infrequently had a pulse below 80. This we regard as a strong point in differential diagnosis between these influenzal pneumonias and those of pure pneumococcic origin.

"The disease was a veritable plague. The extraordinary toxicity, the marked prostration, the extreme cyanosis and the rapidity of development stamp this disease as a distinct clinical entity, heretofore not fully described.

"It is entirely different from our previous pneumonia epidemics. It is fair to state that it is primarily a profound, rapidly progressing septicemia and toxemia, in which pneumonia is an important but somewhat secondary factor."

Influenza and Pneumonia in the Year 1917.—Relying solely upon the sick and wounded cards, there was no relation between influenza and pneumonia in 1917. There are some most competent medical officers who believed that influenza was prevalent in an unrecognized form in the camps in the Fall of 1917, and that a large percentage of the cases of pneumonia occurring at that time were preceded or ushered in by influenza. This belief is apparently founded upon the observations of one or two men, and can be proved or disproved in no way so far as I can see.

Taking the sick and wounded cards for 1917 we can construct the following table:

PNEUMONIA AS A SEQUEL TO RESPIRATORY DISEASES

(All troops in United States in 1917)

PRIMARY DISEASES	NO. OF CASES	NO. OF CASES FOLLOWED BY PNEUMONIA	% OF CASES FOLLOWED BY PNEUMONIA
Measles	47,573	2,075	4.37
Scarlet fever	1,966	54	2.75
German Measles	8,982	39	0.43
Bronchitis	41,233	20	0.049
Influenza	32,248	19	0.059
Meningitis	1,027	13	1.27
Tonsillitis	43,021	7	0.016
T. B. pulmonary	6,799	6	0.088
Laryngitis	4,633	2	0.043
Diphtheria	1,163	1	0.086
Mumps	21,725	0	0.000
Pharyngitis	8,096	0	0.000

In contrast to the above, the following table gives the numerical relation between influenza and pneumonia during the four months of September, October, November, and December, 1918:

Number of cases of influenza	338,343
Number of cases of influenza followed by pneumonia	50,700
Number of deaths from influenza-pneumonia	17,700

INFLUENZA AND PNEUMONIA AS REPORTED IN THE UNITED STATES VITAL STATISTICS FOR EACH YEAR INCLUDING AND SINCE THE YEAR 1900

YEAR	ANNUAL DEATH RATES FROM PNEUMONIA	INFLUENZA	COMBINED DISEASES
1900	158.6	22.8	181.4
1901	133.5	32.2	167.7
1902	124.7	10.1	134.8
1903	122.6	18.5	141.1
1904	136.3	20.2	156.5
1905	115.7	18.8	134.5
1906	110.8	10.3	121.1
1907	120.8	23.3	144.1
1908	98.8	21.3	120.1
1909	96.3	13.0	109.3
1910	147.7	14.4	162.1
1911	133.7	15.7	149.4
1912	132.3	10.3	142.6
1913	132.4	12.2	144.6
1914	127.0	9.1	136.1
1915	132.7	16.0	148.7
1916	137.3	26.4	163.7

Epidemic of Influenza in 1915-16.—During the year 1916, as is seen from the table, the annual death rate from influenza as reported, reached the rate of 26.4 per 100,000. The literature of that time shows that this epidemic originated in the West, first attracted attention in Denver, and gradually spread over the country.

Dr. Dublin of the Metropolitan Life Insurance Company gives the following table in which the deaths from influenza and pneumonia during the months of December, 1914, and January, 1915, are compared with deaths from the same cause during the months of December, 1915, and January, 1916:

NAME OF CITY	DEATHS REPORTED AS DUE TO INFLUENZA		DEATHS REPORTED AS DUE TO PNEUMONIA	
	In 15-16	In 14-15	In 15-16	In 14-15
Baltimore	57	12	219	101
Cincinnati	81	2	105	84
New Orleans	97	44	35	29
New York	494	62	2067	1207
Philadelphia	324	62	564	272
Providence	38	3	31	31
TOTAL	1091	185	3021	1733

Dr. Dublin states that the Industrial Department of the Metropolitan Life Insurance Company covering the entire country and embracing ten millions of people, had deaths in the periods above mentioned as follows:

In December, 1914, and January, 1915 the number of deaths attributed to influenza was 165

While in the corresponding months of 1915-16, the deaths attributed to influenza were	957
The deaths attributed to pneumonia in December, 1914, and January, 1915, were	1468
While the number of deaths attributed to the same cause in December, 1915, and January, 1916, was	2563

Coffey and others have reported an epidemic of influenza at Worcester, Massachusetts, during the first three weeks of January, 1916. During the first three weeks of January, 1915, there were reported in the city of Worcester, twenty-two deaths from respiratory diseases, making a total of 14.9 per cent of the total deaths. In the same period of 1916 there were reported in the city of Worcester, ninety-three deaths from acute respiratory diseases in the same population.

The Relation of Influenza and Antityphoid Vaccination Reactions.—In a general way severe reactions of antityphoid vaccinations resemble in symptomatology, influenza. This led to the suspicion on the part of many medical officers that antityphoid vaccinations in some way increased the susceptibility to influenza. Indeed, some went so far as to say that antityphoid vaccination caused influenza. On account of this suggestion, antityphoid vaccination was discontinued for a time after the appearance of the epidemic of influenza in the Fall of 1918. There were, therefore, entire organizations in which antityphoid vaccination was not practiced. These organizations suffered quite as severely as those which submitted to the vaccination.

The following is an abstract from a report made by the Camp Surgeon at Grant:

"The organizations which suffered most severely were the 5th Limited Service Regiment, the 1st Training Unit and the 13th Training Battalion. These organizations practically were made up of the September increments. Inoculations of new recruits were discontinued. None of the men of the 13th Training Battalion received inoculations and still 3.9 per cent of this command died of pneumonia following this disease. The difference in mortality rate between the 5th Limited Service Regiment, the 1st Training Unit and the 13th Training Battalion, is slight; but the difference between these three organizations and the others is well marked. That the new recruit is more susceptible to this disease and is more apt to succumb than the man who has been trained and accustomed to army life, there is no doubt."

—*V. C. V.*

Pulmonary Tuberculosis and Postural Treatment

IT was pointed out by Webb, Gilbert and Forster that the victim of pulmonary tuberculosis was not infrequently observed resting and sleeping on the side of the least diseased lung. The more actively tuberculous lung would then be

uppermost and so through many long hours be responsible for most of the aeration.

These workers found it of undoubted value to train the consumptive to sleep and rest on the side of the more actively tuberculous organ.

Colonel G. E. Bushnell, M.C., U. S. Army, called the attention of the writer to an observation easily made with the fluoroscope. With a subject lying on one side and the x-ray apparatus properly adjusted the movements of the diaphragm and thorax can be readily studied.

It is noticed that the upper ribs of the recumbent side are pressed together and that there is little motion of this part of the chest wall. Below, however, the diaphragm is noticed to make a far greater sweep on the recumbent than on the upper side.

If the tuberculous lesions are limited to the upper lobe as is usually the case or even should they extend to the apex of the lower lobe, rest of the individual lung by posture would certainly be indicated. In addition the more rapid flow of lymph produced by the greater movement of the diaphragm on the recumbent side would tend to safeguard the lower lobe from tuberculous involvement.

Positive basal lesions, rare except in advanced pulmonary tuberculosis would conceivably be harmed by such postural therapy.

The simple question of the side preferred for rest and sleep has never been properly studied in regard to the pneumonias, bronchiectases and other chest conditions.

The study of the chest movements in different postures by means of the fluoroscope is worth the while and the time of all clinicians who interest themselves in pulmonary conditions.

—*G. B. W.*